The Oxford Medicine

BY VARIOUS AUTHORS

VOLUME III

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CHAPTER I

THE ESOPHAGUS

By E. S. Emery, Jr.

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GENERAL CONSIDERATIONS

Although the structure of the esophagus is admirably adapted to the purpose of conveying food promptly to the stomach, its anatomical relationships and complicated nervous requirements make it more susceptible to outside influences than many of the viscera. An adequate understanding of the disorders affecting the esophagus requires a knowledge of its fundamental anatomy and physiology. Disturbances of the adjacent organs are prone to involve the esophagus by direct contact. A smooth adjustment between the voluntary act of starting food into the esophagus and the autonomic disposal of it to the stomach requires a complicated nervous innervation which is easily influenced by extrinsic factors.

Anatomy of Esophagus

The esophagus starts at the lower border of the cricoid cartilage opposite the sixth thoracic vertebra and ends three quarters of an inch below the diaphragm at the twelfth thoracic vertebra. Although actual measurements are not so necessary as before the days of the x-ray when a bougie was the only means of locating a lesion, it is still useful to remember that the distance from the incisor teeth to the upper end of the organ is six inches, eleven inches to the crossing of the left bronchus and sixteen inches to the cardia.

Its structure is similar to the rest of the gastrointestinal tract in having two muscular layers, an outer longitudinal and an inner circular one. It differs from the rest of the gastrointestinal tract by the fact that the proximal one half is made up of striated muscle, only the distal portion containing the smooth variety. The entire structure is lined with mucous membrane, the epithelium of which is thick and stratified like that of the pharynx. Because the general anatomical relationships may be obtained from any textbook of anatomy, space will not be devoted to them here.

Contrary to former ideas there is now considerable question about the human cardia being a true sphincter. In a study of 150 autopsied cases Lendrum[1] was unable to demonstrate any special band of muscle fibers

marked off by partitions of connective tissue as occurs at the pylorus In a few cases there seemed to be a diffuse thickening of the muscle at the gastric orifice but in most of the subjects there was no localized muscular thickening of any kind However the x ray reveals a definite narrowing at the junction of the esophagus and stomach of a sufficient degree to slow the entrance of material into the stomach In support of a probable sphincteric action it has been noted that the bat much of whose digestion like that of man is done in an upright position has a distinct cardiac sphincter From the available evidence it seems probable that the human cardia has some sphincteric action although not to the same degree as the pylorus

Physiology of Esophagus

The esophagus is innervated by both the parasympathetic and sympathetic nerves in addition to Auerbach s plexus Swallowing is a complicated reflex and involves so far as the pharynx and upper esophagus are concerned the afferent fibers of the glossopharyngeal trigeminal vagus and its superior laryngeal division and the motor fibers of the hypoglossal trigeminal glossopharyngeal vagus and spinal accessory nerves This adequate mechanism will force fluids to the cardia within 0 1 second whereas solids require the aid of a peristaltic wave and take from 2 to 4 seconds to travel the entire course It may then require another 2 to 4 seconds for the solid material to pass the cardia

The motor function is affected markedly by the behavior of the autonomic nerves Many years ago Cannon[2] showed that cutting the vagi produced complete tonelessness of the lower esophagus for 12 to 24 hours after which tone began to return However Knight s[3] studies suggest that the lower esophagus remains dilated after vagotomy unless the sympathetic innervation is overcome by removing the celiac ganglion Perhaps the difference in these results can be explained by the fact that the investigators used different kinds of animals

Our knowledge about the nervous control of the cardia is somewhat vague but there is reason to believe that it is supplied by activating and inhibitory nerves Some observations suggest that the vagus supplies both activating and inhibitory fibers in addition to the inhibitory nerves which come by way of the celiac ganglion According to McSwiney[4] Langley and May observed relaxation on stimulation of the vagus nerve whereas both Klee and Koennecke noted contraction Carlson and later Veach decided that the cardia responded much as the gastric musculature does

Irrespective of the uncertain rôle which the individual nerves play definite reflex effects on this region have been observed Under normal circumstances there is a reciprocal action between the esophagus and stomach so that with swallowing the intragastric pressure drops to almost zero[5] This adjustment wholly disappears after the vagus nerves are rendered inactive Carlson Boyd and Pearcy[6] found that in lightly anesthetized or decerebrate dogs stimulation of sensory nerves in other parts of the body produced reflex changes in the cardia Stimulation of sensory nerves of the mouth pharynx and esophagus results usually in inhibition followed by contraction when the vagi are intact whereas stimulation of the abdominal viscera causes contraction even when the vagi were cut Similarly stimulation of the gastric mucous membrane temporarily inhibits the cardiac tone in unanesthetized dogs Any disturbance of these reflex activities could interfere easily with the normal behavior of the esophagus

Incidence of Esophageal Disorders

Esophageal disorders differ markedly in their relative importance depending upon their seriousness and the frequency with which they occur Adequate statistics on their incidence are hard to obtain because physicians refer patients with obvious and acute lesions to special clinics the figures from which show an unduly high incidence of such conditions whereas the general clinic will receive a greater proportion of the less easily recognized diseases In Boston the Massachusetts General Eye and Ear Infirmary tends to get those patients with obvious esophageal symptoms and the Children s Hospital sees a large proportion of congenital lesions However a general idea of the incidence may be obtained by comparing the relative frequency of esophageal lesions as they occurred in 102 patients at the Peter Bent Brigham Hospital (Table I) and in 878 patients studied at the Massachusetts Eye and Ear Infirmary (Table II)[7]

Table I The Incidence of Esophageal Lesions in 102 Patients Studied at the Peter Bent Brigham Hospital

	Per cent
Carcinoma	42
Diverticulum	22
Cardiospasm	14
Varices	12
Foreign Body	5

Peptic Ulcer	2
Congenitally Short Esophagus	1
Fibrosis	1
Congenital Web	1

Table II The Incidence of Esophageal Lesions in 878 Patients Complaining of Dysphagia Studied at the Massachusetts Eye and Ear Infirmary

	Per cent
Carcinoma	40
Fibrosis lower third	15
Webs	13
Fibrosis upper third	11
Paralysis	6
Burns	5
Pulsion Pouches	4
Extrinsic Causes	3
Ulcers	2
Traction Pouches	1

Carcinoma heads the list at both places with an incidence around 40 per cent At the Massachusetts Eye and Ear Infirmary cardiospasm is termed fibrosis of the lower third and shows the same frequency as at the Peter Bent Brigham Hospital namely 15 and 14 per cent Diverticula (pouches) represent only 5 per cent at the Eye and Ear Infirmary as opposed to 22 per cent at the Peter Bent Brigham because at the former they have listed only those lesions giving symptoms The reason for the higher incidence of webs and fibrosis in the upper third at the Eye and Ear Infirmary is not entirely clear The tables show that carcinoma and cardiospasm continue to be the two most serious disorders which are encountered commonly

Symptoms of Esophageal Disorders

Esophageal symptoms are characterized by the constancy with which they are present substernally and the accuracy with which pain usually is located at the point of involvement Patients with lesions of the upper middle and lower esophagus ordinarily point to the upper middle or lower sternum to signify the location of the discomfort The quality and intensity of the distress varies over wide limits but may not signify anything regarding the seriousness of the trouble One is not justified in ignoring a patient s symptoms because of their mildness

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The intraesophageal lesions which obstruct are (1) tumors which most frequently are cancers, (2) cicatrices, (3) spasms, (4) impaction of foreign bodies, (5) diverticula.

Carcinoma of the Esophagus

General Statistics

As previously pointed out, carcinoma of the esophagus represents 40 per cent. of all esophageal lesions. According to Mosher and MacMillan[1] the death rate is 4 per 100,000 population. Various writers report that it accounts for 1 to 7 per cent. of all cancer deaths. At the Peter Bent Brigham Hospital it occurs in approximately one out of every ten cases of cancer of the gastrointestinal canal and represents 2.5 per cent. of all organic disease of the tract. It is by all odds the most frequent serious disease of the esophagus.

About 10 per cent. of the lesions occur in the upper or cervical portion of the esophagus and 40 per cent. in the midzone near the bifurcation of the trachea and 50 per cent. at the lower end.

The etiology is unknown but is presumably the same as for cancer elsewhere. There is no conclusive evidence for an hereditary factor. It is rarely observed before the age of 40 and is encountered most often between the ages of 50 and 70. It occurs more frequently in the male sex. In some individuals the disease begins in the stomach near the cardia and involves the cardia by direct extension causing the same obstructive symptoms as when the neoplasm begins in the lower part of the esophagus near the cardia.

Two types of lesions occur: the squamous celled epithelioma and the adenocarcinoma. The growths spread along the tube for a distance of 1 to 5 inches and tend to surround and gradually to obstruct the lumen. Some tumors involve the mucous membrane with an accompanying ulceration early in the disease, whereas others limit their growth, at least for a long time, to the outer layers of the esophagus. A knowledge of this difference in behavior helps one to understand the variations in symptoms.

Postmortem examinations may reveal extensive metastases. The lungs are involved often either by direct extension or by metastatic implantation. In addition, the liver, kidneys, adrenals, retroperitoneal lymph nodes and even the skin may be seeded with nodules. If adequate steps are taken to circumvent the obstruction of the esophagus, death comes gradually from the metastases. Occasionally a gross hemorrhage causes a rapid exitus.

Heartburn is associated with esophageal spasm Although it is usually the result of nervousness it may come from organic disease and should never be ignored

Next to heartburn the symptoms which are encountered most frequently result from some form of obstruction These are numerous and any one or all may be present in one individual Impaired deglutition often is noted Swallowing becomes difficult uncomfortable or both Many patients experience a choking sensation others notice only that they are compelled to eat slowly Regurgitation may occur during or after a meal and should be distinguished carefully from vomiting because regurgitation is important evidence for esophageal disease and vomiting is not Nausea rarely is present Pain is a very variable symptom in its incidence and quality Patients describe a slight fulness or intense distress a dull sharp or cutting pain of a continuous or jabbing quality depending upon the nature and extent of the disorder

Examination of the Patient

A careful physical examination is indicated because it may afford evidence which indirectly assists in a correct diagnosis When an obstructive lesion of the esophagus is suspected much may be learned by watching the patient eat After the first few mouthfuls obvious difficulty in swallowing may develop The patient masticates longer and swallows more slowly and with increasing effort

Special methods of study by the x ray and esophagoscope are invaluable aids to diagnosis and any patient with suspected disease of the esophagus should be examined under the fluoroscope Yet both these methods of examination have their limitations even in the hands of experienced operators These limitations will be elucidated in more detail during the discussion of specific diseases but it is worth noting that in certain cases the symptoms may be more helpful than the x ray or esophagoscopic findings

Virtually all esophageal disorders interfere with the passage of food and produce dysphagia The causes of stenosis are divided into (1) anatomical disease of the esophagus or adjacent structures (2) spasmodic contraction of its muscular fibers or (3) impaction of foreign bodies

Numerous extraesophageal lesions may obstruct but are encountered only rarely These are aortic aneurysm mediastinal growth distended diverticulum of the pharynx pericardial exudate dilated left auricle diseased vertebrae enlargement of the thyroid and cervical lymph nodes and retropharyngeal tumors

There are other symptoms which should be watched for. Regurgitation will develop with sufficient obstruction. Hoarseness or a chronic cough accompanies lesions in the upper end of the esophagus. Sometimes hiccoughs develop in the later stages. The occurrence and severity of bleeding depend upon the amount of ulceration. Hematemesis is not common, occurring in about 10 per cent of the cases. Blood is found in the stools in a higher per cent but occurs only if the lesion has broken through the mucous membrane.

Diagnosis

The insidious nature of the disease makes for a late diagnosis. Statistics show that approximately one fifth of the patients have symptoms for one year or more and another one fourth from six months to one year before the condition is recognized. Somewhat earlier diagnoses could be made if physicians appreciated the significance of the early symptoms and observed their patients more closely.

Because there are no typical symptoms in the early stages, recourse must be made to laboratory procedures, particularly roentgenology and esophagoscopy. Both are helpful and should be used frequently when an esophageal lesion is suspected. However, they are not infallible. In the writer's experience the x-ray is misleading in about 8 per cent of the cases. The usual error is one of an erroneous interpretation rather than completely missing the lesion. Occasionally an intramural growth will produce irritability before impinging on the lumen, and the same is true if the growth merely surrounds the esophagus. Under these circumstances the x-ray will reveal no abnormal findings unless the organ happens to be irritable at the time of the examination, when it will show only spasm. Because this type of involvement can originate from a gastric cancer, a careful examination of the stomach always is indicated when a suspected esophageal involvement is not found.

Under similar conditions the esophagoscope also will fail to reveal the lesion. A positive biopsy clinches the diagnosis, but a negative biopsy is of little value. It is easy for an operator to snip only normal mucous membrane covering the surface of a tumor which is expanding into the lumen. In 21 patients of the series on which esophagoscopy was performed an incorrect diagnosis was made in 2. In one the lesion appeared benign to the operator and normal tissue was removed. The lesion was not found in the second patient. In two others the operator found and diagnosed the nature of the lesion but removed only normal tissue for biopsy.

Symptoms

The characteristic story is a gradually increasing obstruction At first the larger pieces of food stick which occasions slight attention for the sensation is similar to that experienced with rapid eating and insufficient mastication Dysphagia becomes increasingly frequent and occurs with smaller and smaller substances until swallowing is difficult for anything but liquids This story is in contrast to a spasmodic obstruction which does not depend upon the coarseness of the swallowed material An accurate history of gradually increasing obstruction is on this account of extreme diagnostic importance

Unfortunately all esophageal carcinomata do not give this typical history which was obtained from only 58 per cent of the patients in a series studied by the writer If a patient is seen early in the disease a certain amount of time must elapse for the characteristic story to develop Moreover the growth of some tumors irritate before they obstruct at this time the patient s symptoms result from spasm These may be sufficiently prominent to mask the symptoms which come from a gradual encroachment on the lumen

A differential diagnosis between carcinoma and cardiospasm may be difficult particularly as an x ray examination reveals only spasm in those cases in which the carcinomatous lesion does not involve the lumen For this reason it happens not infrequently that carcinoma is diagnosed mistakenly cardiospasm To guard against this error it is necessary to detect any symptoms indicative of increasing obstruction

Dysphagia is the most frequent symptom and occurred in 99 per cent of 61 patients studied at the Peter Bent Brigham Hospital Pain was the next most frequent occurring in 62 per cent The quality of pain varies greatly in different individuals and is not characteristic Some describe it indefinitely as discomfort some as a burning distress Occasionally it is so intense as to require morphine to alleviate it

In the majority of cases the pain is located close to the lesion but this is not always true and the pain may not suggest trouble with the esophagus The location of the pain agreed with the position of the lesion in 25 of 38 patients of my series Six patients with a lesion at the cardia had discomfort in the midepigastrium and one at the umbilicus It is possible that the disease in these cases started in the stomach and later involved the cardia Five patients with a cancer in the middle third of the esophagus had pain only in the epigastrium In one case a lesion in the middle third produced pain only in the back

With a history of typical increasing obstruction it is usually safe to diagnose carcinoma in spite of an x ray report of cardiospasm or a negative biopsy

Prognosis

The outlook is virtually hopeless Most patients live from six months to one year after the diagnosis is made A small number live from one to several years

Treatment

Surgical Removal — Recent improvement in the technique of thoracic surgery has renewed interest in the possibility of removing esophageal carcinoma The development of the transpleural approach has simplified the exposure of the lower esophagus and upper stomach and tends to lower the immediate operative mortality Notwithstanding improvements in surgical procedures the chances of cure are remote usually because of the advanced stage of the disease at the time of diagnosis

Before 1934 only one case survived operation more than two years Thirteen other technically successful operations are on record but the patients died of recurrence or metastases Since 1928 twelve American surgeons have reported successful resections on 34 patients 20 of whom were living in 1941[9] Radical surgery should be attempted only after a careful study has ruled out metastases and after warning the relatives of the seriousness of the operation

For most patients the object of treatment still remains to afford the individual a maximum of comfort during his last days In addition to providing sufficient fluids and nourishment it is necessary to prevent accumulation of mucus by keeping the esophagus open

A judicious choice of gastrostomy dilatation and roentgenotherapy furnish the best results Although gastrostomy alone maintains an adequate dietary intake and is indicated in states of severe starvation it does not alleviate obstruction The patient is harassed by the accumulation of mucus above the point of constriction Being very viscid the mucus is difficult and often impossible to expel before the esophagus fills to the laryngeal orifice so that the individual is constantly choking from his own secretion Although some persons can be taught to irrigate the esophagus with a dilute solution of sodium bicarbonate the procedure is annoying and difficult Furthermore life is more enjoyable for the patient who is able to eat in the company of family and friends

Sarcomas —The sarcomas vary widely in their malignancy but in general two types of fibrosarcoma are encountered[11] The first is circumscribed and has a broad base which is overlaid with polyps with distinct pedicles It grows slowly to a size of from 1 to 7 cm and shows little tendency to metastasize This kind seldom causes stenosis The second kind is much more malignant It grows rapidly infiltrates deeply and ulcerates extensively Because of its large growth it obstructs the esophagus by surrounding and penetrating the lumen It may compress the trachea and produce edema of the larynx Necrosis gangrene bleeding and perforation may accompany their growth This kind metastasizes frequently to lymph nodes bones and other viscera

Sarcomas have been reported at all ages from 4 to 80 most of them occurring after the fourth decade

In general the symptoms as a result of gradual obstruction are similar to those of carcinoma However they seem to differ from carcinoma in producing considerable pain which makes an early appearance is piercing in character and frequently radiates between the shoulder blades Deep seated pain may simulate a pulmonary condition or an aneurysm Also these tumors have a tendency to bleed earlier in their course than carcinomata

The x ray appearance is similar to carcinoma A differential diagnosis can be made most efficaciously by a biopsy The treatment is the same as for carcinoma Other malignant tumors which have been reported in the esophagus are lymphosarcomas melanotic sarcomas and leiomyosarcomas

Varices of the Esophagus

The veins of the lower esophagus become dilated in patients with decompensated hearts and in the presence of obstruction of the portal vein as occurs with cirrhosis of the liver and hepatosplenomegaly Severe or fatal hemorrhage may follow an erosion The diagnosis is made on the history of bleeding and the finding of the cause from a study of the patient The x ray may reveal the presence of widely dilated veins if a thick paste of barium is allowed to trickle through the esophagus There is no cure for the condition Their injection through the esophagoscope with sclerosing solutions has given indifferent results

Cicatricial Strictures of the Esophagus

Cicatricial stenoses may develop at any level but are found usually in the upper and lower thirds of the esophagus The commonest cause

They vary from 8 x 10 centimeters to 12 x 15 centimeters in our experience

The changes following such intensive radiation can be divided into three stages The first is engorgement and swelling which may increase the dysphagia for a few days Therefore gastrostomy should be considered previous to irradiation for a badly starved patient The second stage is resolution with a disappearance of the dysphagia and in some instances a return to a normal radiographic appearance After a period of weeks or months the formation of scar tissue produces further constriction this can be controlled by dilatation

This treatment does not cure and may not prolong life as all our patients have died from metastases or direct extension of the growth However it can completely destroy the original lesion as proved by some of our autopsied cases The advantage of the method is that it is a painless way of keeping open the esophagus until death comes from the metastases The only unpleasant symptom is the malaise which accompanies any intensive roentgen therapy Our greatest difficulty has been to convince the patient of the need for dilatation to prevent the later tendency toward constriction Roentgen therapy is indicated particularly for the cauliflower type of growth which cannot be controlled satisfactorily by dilatation alone

Other Tumors of the Esophagus

Tumors other than carcinoma receive little clinical attention because they develop in the esophagus so rarely However virtually all types have been reported most of which are benign

Benign Tumors — Myomata are the commonest of the benign tumors Rarely do they become large enough to give symptoms and ordinarily are found during postmortem examinations Other benign tumors are adenoma papilloma hemangioma hemangio endothelioma and lipoma They may obstruct frequently become pedunculated and sometimes are regurgitated into the mouth Watson Williams[10] reported a death from strangulation as a result of aspirating a polyp Under the x ray the benign tumors produce a smooth filling defect which may shift its position

The diagnosis is made on the history of dysphagia or the regurgitation of the tumor and the characteristic x ray appearance

Pedunculated tumors can be snipped out through the esophagoscope Radium implants may be used for tumors the excision of which is impossible

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CICATRICIAL STRICTURES OF THE ESOPHAGUS

Cicatricial stenoses may develop at any level but are found usually in the upper and lower thirds of the esophagus The commonest cause

of these strictures used to be the swallowing of caustic alkalies and strong acids which at one time ranked second among the causes of stenosis. However this is no longer true for which much of the credit is due to education of the public against the danger of burns and to legislation which requires various drugs and commercial products to carry labels warning against the danger of ingestion. At present from 5 to 10 per cent of esophageal lesions are caused by this condition.

Cicatrices have resulted from the healing of ulcers following typhoid fever and other chronic infections. Although impaction of foreign bodies and acute infections have been known to cause constriction, this does not usually happen. It is not quite clear just what governs the formation of these strictures. Although involvement of the submucous layers is necessary for fibrosis and contraction to occur, ulcerations are not always followed by contraction. Conversely, many patients with cicatricial stenosis do not give any history of previous esophageal symptoms.

Corrosive Lesions. — The appearance of patients seen shortly after the ingestion of a corrosive substance will vary with the amount and strength of the swallowed material. Nearly all will show some evidence of burns about the lips and mouth. Substernal and epigastric pain is intense, the patient rolling about in agony. Severe burns will produce a state of prostration or shock. Later symptoms depend upon the development of a cicatrix. The interval between the initial trauma and the development of obstruction varies widely in different cases. In Vinson's[12] experience the onset of obstruction usually is within 6 to 8 weeks and obstruction progresses rapidly. However a latent period of months to years may exist before obstruction takes place. Most of these strictures arise at the lower end of the esophagus where the corrosive solutions are held up by the retarding influence of the cardia.

The symptoms are progressive dysphagia and may be quite similar to carcinoma. A differential diagnosis is not always easy, particularly if the obstruction develops in middle life and years after the burn was sustained. The x-ray reveals a smooth fusiform narrowing but unfortunately carcinoma may also simulate this appearance. However there are two helpful considerations when doubt exists about which of the two conditions is present. A history suggesting an element of spasm favors carcinoma. A cicatricial stricture is more likely to be located some distance proximal to the cardia, a condition which can be determined easily by the x-ray.

Treatment. — By the time a physician sees one of these patients it is usually too late for any antidotes to be effective, although the administration of a large amount of olive oil is recommended very often.

General symptoms should be taken care of first morphine for pain and appropriate measures for combating shock As the danger of a spreading infection is very real the giving of one of the sulfonamide drugs should be considered

Everything by mouth should be forbidden for a period of 7 to 10 days with the exception of the original dose of olive oil After this one can begin initial feedings of small amounts of bland liquids and increase the diet as the patient s condition indicates

It is important to start dilatation at an early date because it is much easier to prevent a cicatricial stricture than to overcome it Vinson recommends the swallowing of a silk thread immediately after the inflammatory swelling has subsided Dilatation is accomplished best by one of the olive shaped bougies If this is started before extensive contraction has developed a moderate sized instrument size 30 French should be introduced This is followed in 7 to 10 days by a slightly larger one From then on a program should be instituted which includes routine dilatations with increasingly larger instruments No set rule can be laid down for the time interval between dilatations but care should be taken not to allow an unduly long period to elapse The tendency to contract is marked and persistent Dilatations should be performed every few days until the desired lumen is reached This may be maintained by dilatation at longer intervals It is important to acquaint the patient with the persistent tendency of the lumen to shrink so that he or she will not neglect necessary treatment

Dilatation is not an unduly discomforting procedure and cases of cicatricial stricture can be controlled adequately with a combination of sufficient interest on the part of the physician and intelligent cooperation on the part of the patient

Stricture in Upper Third of Esophagus — Strictures in the upper third of the esophagus develop slowly the patient having had symptoms of dysphagia for some years before seeking advice Presumably all of them follow a previous trauma or infection but many individuals are unable to recall such an incident Usually the only symptom is an inability to swallow a large bolus

The diagnosis is made by x ray and esophagoscopic examination X ray studies show a smooth fusiform narrowing with a normal mucosal pattern Direct visualization through the esophagoscope reveals the smooth constriction and a normal mucous membrane

Dilatation is not very effective as determined by subsequent roentgen examinations although the patients seem to experience some relief

Esophageal Webs

In another group of patients with dysphagia the x ray reveals an abrupt sharply defined narrowing in the upper third Esophagoscopic examination shows that the lumen is narrowed by a web or diaphragmatic like stricture with a central or eccentric opening Many of these patients give a history of having swallowed a foreign body or of a superficial ulceration about the mouth or pharynx at some time previous to the onset of dysphagia These webs involve only the mucous membrane and can be easily stretched or broken by instrumentation Such an operation provides striking relief

Esophagitis

Esophagitis is an ill defined subject about which our knowledge is scanty Particularly is this true of the mild cases in which the symptoms are indefinite and our means of investigation are limited to esophagoscopic observation A minority of these cases come to autopsy in these often it is impossible to distinguish postmortem changes from those which have existed during life

Cases may be divided into two groups depending upon whether ulceration exists Simple inflammatory changes may occur from excessive indulgence in alcohol and perhaps from highly seasoned foods Angioneurotic edema of the esophagus has been described and there is some evidence to suggest that the organ at times becomes allergic Acute infection with the pyogenic organisms undoubtedly occurs but the so called chronic esophagitis from foci of infection such as the teeth, tonsils gallbladder etc appears to the writer as a debatable point

Acute Non ulcerative Esophagitis

The symptoms of acute non ulcerative esophagitis depend upon the cause and the severity of the process Substernal burning or heartburn is the most frequent complaint and a sense of fulness may be experienced True pain which becomes intense on swallowing occurs in patients with marked inflammatory changes

The diagnosis of the non ulcerative types is made on the symptoms and a history of a probable cause together with evidence of inflammatory changes seen through the esophagoscope

Therapy should be directed toward the prevention or relief of the cause when the latter is known Alcohol should be interdicted, and a

soft bland diet prescribed Temporary relief sometimes may be obtained by having the patient sip milk or dilute solutions of sodium bicarbonate Swallowing about a gram of one of the local anesthetics such as ethylamimobenzoate with a small amount of water sometimes will relieve the more intense symptoms

Specific Infections of the Esophagus

Involvement of the esophagus by specific organisms of a non pyogenic type occurs infrequently Tuberculo is syphilis diphtheria actinomycosis blastomycosis and thrush have been reported

Primary and secondary syphilitic lesions *usually are not recognized* although gumma has been diagnosed a number of times Because of its rarity it is not enough to make the diagnosis on the basis of a filling defect in a known syphilitic Carcinoma of the esophagus must be suspected always even if apparent improvement follows anti syphilitic treatment

The cases in which tuberculosis actinomycosis and blastomycosis of the esophagus have been reported have shown rather extensive involvement of other organs These patients give symptoms of obstruction spasm or irritability X ray studies u ually will reveal an irregularity which taken together with findings of the disease els where is sufficient evidence on which to make a diagnosis

Esophagoscopy *should be utilized when there is any doubt about* the nature of the lesion Primary tuberculosis in the esophagus is quite superficial looks whitish or grayish and is not surrounded by a red zone Tuberculous invasion by suppurating lymph nodes looks more like peptic ulcer but usually is located at a much higher level Blastomycosis *presents a granular eroded or whitish appearance Actinomycosis can* be demonstrated readily by biopsy Thrush is found in poorly nourished or debilitated individuals Local treatment is ineffective and therapy must be directed toward improving the patient s general health

Diphtheric involvement of the esophagus is always a grave affair *and the disease usually proves fatal Treatment is the same as for any* case of diphtheria

Ulcerative Esophagitis

Esophageal ulceration is seen as a result of infection toxemia neurogenic disturbances and pressure from such things as foreign bodies aortic aneurysm etc Peptic ulceration also occurs

Bartels[13] found 82 cases of acute ulcerative esophagitis in a series of autopsies at the Mayo Clinic which represented an incidence of 0 013 per cent The pathological changes could be divided into four groups (1) phlegmonous and pseudomembranous changes (2) simple ulceration with slight or marked inflammation (3) hemorrhagic ulceration (4) phlegmonous changes of the entire wall

Although no specific etiology was determined for the individual cases it was striking that all had died with some debilitating disease or post operatively The condition of many of the postoperative cases had been poor to start with This series suggests that the general condition of the patient may be the determining factor in the development of acute eso phageal ulceration

Cushing[14] reported cases which developed acute ulceration of the esoph agus and stomach after operations in the region of the fourth ventricle suggesting a trophic cause

Patients with chronic uremia may develop ulceration of the esophagus the exact cause of which has never been determined but the general condition of these patients also is not good

The symptoms of acute ulceration are dysphagia and substernal burning which may be present throughout the esophagus Some patients complain of pain high in the epigastrium Vomiting may be troublesome and many of thes patients have hematemesis some in large amounts Perforation can occur and is often symptomless

In the treatment of acute ulcerative esophagitis every effort should be made to improve the patient s general condition A well proportioned liquid or semi solid diet should be prescribed and adequate measures undertaken to overcome any possible deficiency in vitamins Sulfa *diazine is indicated when an infectious process is present or perforation* is feared However its use must be carefully supervised because vomiting is distinctly undesirable

The measures already suggested for the relief of local discomfort may be tried morphine is necessary for those with severe pain Local appli cations of silver nitrate through the esophagoscope are reported as beneficial in cases of a circumscribed ulcerative process Most patients with an esophagitis either get entirely well or die

Peptic Ulcer of the Esophagus

Peptic ulceration of the esophagus makes up about 2 per cent of all esophageal disease Various theories have been expressed concerning the cause of these round ulcers but the idea has gained ground steadily that

their existence depends upon the presence of aberrant gastric mucosa That aberrant mucosa in the esophagus is not uncommon is shown by the finding of Rector and Connerley[1] that some form occurred in 7 8 per cent of 1 000 infants and children the sections having been taken at random from various levels More complete studies should reveal a higher incidence Approximately one fifth of these showed parietal cells none of which occurred in the inferior third of the organ This observation is opposed to the clinical impression that peptic ulceration occurs just proximal to the cardia On the other hand these authors found that inflammation with and without ulceration frequently was present in aberrant tissue even in the absence of parietal cells

In most instances the symptoms reveal the same general characteristics as peptic ulceration of the stomach and duodenum Distress comes on a half hour or longer after eating in some cases only after the heartiest meal of the day The pain may last all night unless stopped by the taking of alkali The prompt relief following alkalies is so marked and constant as to justify the conclusion that the pain in peptic ulcer of the esophagus *is due to acid*

The most constant symptom is pain located behind the lower half of the sternum and extending through to the back between or under the shoulder blades *Local tenderness may develop to the passage of food* and persistent pain may start on swallowing At times the patient may feel food pass over the ulcer The symptoms are not always so suggestive and may be described as a vague substernal burning or soreness

The x ray usually will reveal a local spasm with or without a crater On occasion spasm will develop only with distress the esophagus appearing normal between times Jackson[16] reports that the chief characteristics of the lesion when viewed through the esophagoscope are its flatness the absence of annular infiltration and the absence of exuberant fungations If there is any question about its appearance a biopsy should be taken from the edge of the ulcer This will show the transition from the pathological to the relatively normal structures and cancer can be excluded However in one case known to the writer the gastric cells were mistaken by several pathologists for carcinomatous changes and the report of a carcinoma was made

The general treatment is similar to that of peptic ulceration of the stomach and duodenum Rest bland diet alkalies sedatives etc are indicated Jackson believes that local applications consisting of silver nitrate not stronger than 10 per cent are beneficial given once weekly with interim applications of bismuth subnitrate by esophagoscopic insufflation

Foreign Bodies in Esophagus

All kinds of things may stick in the esophagus and these mishaps may occur at any age Infants and children are prone to swallow shiny objects such as safety pins buttons coins etc Persons in middle age may inadvertently swallow bones or accidentally swallow some object which they have been holding in the mouth such as pins and nails Elderly persons may swallow their dentures and it is surprising how often a large bolus of meat may stick in the esophagus The latter individuals can have the same thing happen repeatedly as though there had developed a disturbance in the mechanism of swallowing which is responsible for this mishap

Usually the patient or the parents of a small child give a history of having swallowed an object or that it feels as though something was "stuck in the throat" As it is important to remove a foreign body as quickly as possible it is incumbent upon the physician to study the patient thoroughly A large object may be visualized through the mouth or with a laryngoscopic mirror if it has stuck at the entrance of or above the esophagus

Objects of fair size which have slipped into the esophagus can be located easily by the roentgenologist if they are opaque to the x rays However fish bones and chicken bones have a density which may not be distinguished from the normal thoracic shadows Also the shadows of small metallic objects such as pins may be obliterated Therefore it is important to make several exposures in different positions in the endeavor to throw these objects into relief At times a swallow of barium will locate an otherwise invisible body The barium adheres to the spot at which the foreign body has lodged If in spite of this the object remains invisible the patient should be esophagoscoped and the presence or absence of a foreign body determined by direct observation

It is important to have a foreign body removed from the esophagus promptly which can be accomplished with comparative ease by an experienced esophagoscopist The manipulation becomes much more difficult and at times virtually impossible the longer the object has been impacted Edema inflammation and infection develop rapidly Visualization becomes difficult and removal is fraught with the dangers of perforation and the spreading of an infection If ulceration develops there may follow cicatrization with narrowing If allowed to go on long enough perforation may occur

Perforation of the Esophagus

As already elucidated perforation of the esophagus may occur from foreign bodies corrosive solutions acute ulcerative conditions and instrumental dilatation

Disorders of the esophagus have appeared to follow external trauma, and Vinson[17] reports one case in which perforation was presumably the direct result of an automobile accident The patient s chest was jammed against the steering wheel following which he suffered severe substernal pain His temperature rose to 102° F Five days later he had difficulty in swallowing and an x ray taken two weeks after the accident revealed a perforation of the esophageal wall

Sudden perforation usually is followed by severe pain beneath the sternum or in the neck Emphysema of the neck follows shortly after perforation high in the esophagus Emphysema of the tissues does not develop so quickly with perforation of the lower end Symptoms of shock and a high temperature develop within a few hours of the injury Acute mediastinitis and pleuritis particularly on the left always accompany an opening of any size

Treatment — As soon is a perforation is suspected or known nothing should be taken by mouth Fluids should be given parenterally morphine for pain and the usual methods taken for combating shock. The sulfonamide drugs are indicated although vomiting is to be guarded against so that they must be used with extreme care The question always arises as to the advisability of attempting to close the rent However the approach is difficult even with rupture of the lower esophagus and stitches do not hold well because of the friability of the organ For these reasons conservative treatment usually is advised The prognosis always is extremely grave

Lacerations of the Esophagus

Weiss and Mallory[18] have reported lacerations and ulceration at the junction of the esophagus and stomach from severe and persistent vomiting The chief clinical manifestations were persistent vomiting and retching frequently precipitated by alcoholic debauches and associated with massive hemorrhages Autopsies revealed two to four fissure like lesions of the mucosa On microscopic examination the fresh lesions were found to be ulcerations of the mucosa extending as deep as the muscular layer

Spasms of the Esophagus

Esophageal spasm was recognized in the 18th century as revealed by the descriptions of Friedrich Hoffmann[19] and Alexander Monro III[6]

In 1821 Purton[1] gave the first clear description of what was later to be known as cardiospasm As the years have gone on we have recognized spasmodic conditions with increasing frequency but our knowledge concerning their cause is limited Owing to the complicated nervous innervation of the esophagus it is to be expected that disturbances in the motor function would be frequent and associated with numerous pathological and functional states of the body Esophageal spasm is known to occur under three conditions (1) as a part of certain definite diseases such as tetanus hydrophobia hysteria chorea and epilepsy (2) in association with certain conditions to which its presence has been attributed through reflex action such as tuberculous ulcers of the larynx diseases of the stomach peritoneum etc (3) in individuals with no recognizable disturbances other than perhaps nervousness

In recent years evidence has been accumulating to suggest that deficiencies presumably of a vitamin nature are responsible for some esophageal spasms

Because few of these patients die as a result of spasm we have learned little about the possible pathological changes and the exact etiology in the individual case For the most part our classification is limited to the location of the spasm and the general appearance of the esophagus under the x ray This reveals that localized spasm most frequently involve the upper and lower ends of the tube Diffuse spasm more often involving the lower third of the esophagus is seen not infrequently

Localized Spasm at the Upper End of the Esophagus

Dysphagia as the result of an inability to introduce food into the upper esophagus is a fairly common complaint and occurs in a variety of conditions

Functional dysphagia may be seen at any age When it occurs in younger persons, usually it is associated with nervousness or hysteria Older persons not infrequently will have difficulty in swallowing in the absence of any neurotic manifestations The exact etiology underlying the dysphagia of the aged has not been determined Dysphagia from a true paralysis comes from a bulbar palsy and although rarely encountered except in acute infections of the nervous system the possibility of its

existence should be kept in mind Also there is reason to believe that dysphagia may be a manifestation of a dietary insufficiency

The disturbance in physiology which occurs with the functional dysphagias may be of two varieties (1) an incoordination of the swallowing reflex so that the food is not propelled normally through the fauces and pharynx (2) a spasm of the cricopharyngeal muscle which obstructs the entrance of the food Statistics on how often each of the two mechanisms occur are so inadequate as to be of little value

Neurotic Spasm of the Upper Esophagus

Patients with a functional spasm of the upper esophagu complain of a lump in the throat the so called globus hystericus The sensation is accompanied by a spasm of the cricopharyngeal muscle which has been observed frequently through the laryngoscope However most recent genological examinations are unable to demonstrate any spasm This agrees with the clinical observation that eating alleviates the sensation temporarily Patients in whom a globus is the only manifestation of the neurosis are not dysphagic and do not fear eating On the contrary the lump in the throat is present when they are not eating In addition to a globus hystericus a certain number of these patients have other neurotic disturbances which cause them to refrain from eating with the result that many physicians incorrectly associate a globus with dysphagia. These patients should be studied carefully by x ray and laryngoscopic examination to eliminate any local disease and to convince the patient of the functional nature of his trouble Treatment should be concentrated on the underlying emotional disturbance

The condition must be distinguished from that encountered in patients whose only symptom is an inability to swallow without any accompanying sensation such as a lump or the sticking of food in the throat The latter trouble is prone to follow some psychic shock or may come with a prolonged nervous strain Watching the patient eat may give a clue to the diagnosis The individual wobbles the food around with the tongue but does not actually swallow Observation under the fluoroscope reveals the food in the anterior portion of the mouth and a failure of the tongue to start the bolus on its way through the pharynx In these cases there seems no reason to suspect a spasm although a satisfactory x ray examination of the pharynx and upper esophagus often is impossible because the patient will not swallow the barium However a careful search for unsuspected pathological lesions always is indicated The writer well recalls a 12 year old child who developed complete dysphagia immediately follow

ing a near drowning catastrophe Because the whole story suggested a functional dysphagia following psychic shock the little girl was treated for more than a week by psychotherapy After it became evident that improvement was not occurring an esophagoscopy revealed distinct webs at the entrance to the esophagus

Treatment consists of eliminating the fear of organic disease and in establishing a sympathetic program for re educating the patient in how to swallow Meals should be free from interruption and in the presence of only the physician Except for the use of mild sedatives if and when they seem indicated drugs should not be used and instrumental dilatation should not be attempted

Dysphagia with an Accompanying Anemia

In 1922 Vinson[90] reported 69 patients from the records of the Mayo Clinic with a functional dysphagia, many of whom showed a marked hypochromic anemia Since then other cases have been reported under such titles as Plummer Vinson syndrome spasm of the upper end of the esophagus syndrome of anemia glossitis and dysphagia, esophageal spasm with severe anemia or simple achlorhydric anemia with dysphagia

These reports have produced an ill defined group of patients in whom the characteristics common to all have been a functional dysphagia of the upper esophagus and a hypochromic anemia Other more variable symptoms and signs are described which with our recent knowledge can be explained by an existing deficiency

Definition — A condition in which there is a functional difficulty in swallowing associated with evidences of a state of deficiency

Etiology — Two views are held as to the cause of this condition According to Vinson it is primarily a neurosis the anemia and other evidences of deficiency following an inadequate dietary intake consequent upon the hysterical dysphagia His conclusion is deduced from the observation that relief of the dysphagia has followed psychotherapy and the signs of deficiency have disappeared with resumption of an adequate intake of food However Suzman[3] concludes that the condition is essentially a deficiency of which the dysphagia is just one manifestation

Sex and Age — The condition is seen much more frequently in females It occurs in the third decade onward but is encountered more often after the age of 40

Pathology — The postmortem findings of one case of Suzman showed hyperkeritinization of the tongue hypopharynx and esophagus Areas of desquamation and atrophic degeneration of the underlying muscle

tissue were present The myenteric plexuses showed no abnormal findings

Symptomatology — The most common complaint and usually the one which troubles the patient most is the swallowing of solid food Little or no trouble is experienced with smooth substances such as milk fine cereals custards etc Meat is attempted only if finely ground and may be refused entirely as is generally the case with vegetables Fruit juices may be feared because the acidity produces burning of the mouth and pharynx Other gastrointestinal symptoms may be substernal pressure abdominal fulness gas in fact those symptoms which occur with functional disorders of the intestines Still other symptoms may be burning of the mouth and tongue anorexia and easy fatigue

Physical Examination — Although many of these patients have had symptoms for a long time they do not show loss of weight owing to an adequate caloric intake However they may show signs of a deficiency Pallor is a frequent finding The tongue often is clean red and appears sore Fissures at the corners of the mouth and a palpable spleen have been reported in many cases

Laboratory studies reveal a marked hypochromic anemia the hemoglobin frequently being 60 per cent or less Many individuals show an achlorhydria Roentgen studies reveal constriction in the cervical esophagus but often the examination is negative Laryngoscopic studies should be utilized to rule out organic disease and should be performed by a trained individual as it is possible to mistake a spasm for a web

Treatment is aimed toward encouraging the patient to eat and building up the general condition The passage of a bougie or stomach tube often is enough to convince the patient of the possibility of swallowing solid food He should be encouraged to take a broad general diet Intensive vitamin therapy is indicated The injections of liver extract at times seem to have a beneficial effect Iron should be prescribed in large doses

Diffuse Spasm of the Esophagus

Occasionally one encounters individuals who are suffering from a diffuse spasm of the esophagus The condition usually involves the distal end for a matter of 4 to 6 inches and frequently is confused with cardiospasm Faulkner[24] reports a spasm of the entire esophagus due to a psychic cause My own cases have always had some disease in the upper abdomen the eradication of which relieved the esophageal disturbance Hence it seems that a frequent if not the only cause of the disorder is a reflex from lesions in other organs

Diffuse spasm produces dysphagia substernal fulness and frequently a good deal of pain Usually the condition produces more pain than cardiospasm The attempt to pass a sound is often unsuccessful owing to the distress which is provoked and the resistance which the esophagus exerts on the instrument

The x ray reveals diffuse contraction of the lower third of the esophagus with a scalloped edge This is the exact opposite of the typical appearance of cardiospasm in which the esophagus is characteristically dilated and shows a smooth edge except for an occasional spasm or signs of peristaltic activity

Diffuse spasm requires a careful search for disease of other organs for which appropriate treatment should be started I have seen a diffuse spasm disappear following the surgical removal of a duodenal ulcer after intensive medical therapy for the ulcer and local treatment of the esophagus had not affected any improvement The local treatment of the condition is similar to that of cardiospasm although the results are not as satisfactory

Spasm at the Cardia

When simple spasm occurs at the cardia the patient experiences a feeling of fulness at the lower sternum accompanied by a sensation of food lodging there This is similar to what probably most of us have felt at some time when eating hurriedly or under tension After a few minutes the food passes into the stomach with accompanying relief Simple spasm at the cardia is characterized by the short duration of the attack and the generally intermittent character of the symptoms If the patient is x rayed during an attack the barium is seen to be held up by a smooth constriction at or just above the cardia with no or very slight dilatation above the area of constriction Ordinarily no cause other than possible nervousness can be found to explain the condition, although at times an abdominal lesion suggests a reflex cause Usually the condition is not very troublesome and is controlled easily with the use of sedatives and antispasmodic drugs such as atropine An occasional patient with more persistent symptoms may need to be dilated with a bougie size 60 French

It is important not to confuse this condition with more serious lesions at the cardia Carcinoma peptic ulcer and a local esophagitis from any cause may produce spasm in this area and should be distinguished from simple spasm Early cardio pasm may give rather similar symptoms and appearance under the fluoroscope Verbrycke[5] believes that most patients

with simple spasm at the cardia later will show evidences of true cardiospasm an idea with which Vinson[6] disagrees I agree with Vinson and believe that the error is made frequently of mistaking a simple spasm at the cardia for cardiospasm

Idiopathic Dilatation of the Esophagus

Synonyms — Cardiospasm achalasia of the cardia diffuse dilatation of the esophagus without anatomic stenosis hiatal esophagismus simple ectasis of the cardia phrenospasm congenital dilatation of the esophagus The numerous synonyms indicate the general uncertainty concerning the nature of the disorder It is discussed under the spasms partly because of its historical associations and because the symptoms suggest that a spasmodic factor is involved

Definition — A condition of uncertain etiology which results in the development of varying degrees of esophageal dilatation and in a failure of the esophagus to empty normally

Incidence — Idiopathic dilatation is a comparatively rare condition Forty records were found in the Peter Bent Brigham Hospital of which to my mind only 34 seemed to fulfill the diagnostic requirements of idiopathic dilatation as opposed to simple esophageal spasm These 34 patients were seen over 26 years making an incidence of 1 3 patients per year The condition occurred once in approximately 2 600 patients although some clinics report a somewhat higher incidence It represented 13 8 per cent of all esophageal diagnoses made at our hospital and 0 8 per cent of organic disease of the gastrointestinal tract

Etiology — The theories on etiology have been deduced from the observation that food fails to pass normally into the stomach and that the esophagus becomes dilated proximal to the cardia In 1882 Von Mikulicz[7] concluded from his studies with the rigid esophagoscope that the primary difficulty was a spasm of the cardia and that the dilatation was secondary to the obstruction His terminology of cardiospasm has continued although modern esophagoscopists have not confirmed its existence Their failure to do so has led others interested in the subject to postulate an imbalance of the vegetative nervous system with an incoordination between the lower esophagus and the cardia In 1922 Mosher[8] advanced the idea that the obstruction was the result of pressure by the liver and Jackson[9] that the esophagus became pinched by a contraction of the diaphragmatic crura

However the histological studies of the English school[10] which have shown a disintegration of Auerbach s plexus in the dilated portion of the

esophagus have renewed interest in the concept of an incoordination between the esophagus and cardia Lendrum's[1] observations in this country have confirmed the work of the English investigators which now is accepted generally as the cause of the trouble However final proof is still lacking Experimental studies appear conflicting and do not seem to explain all the clinical signs and symptoms

Knight[3] was able to produce in cats the radiographic appearance of cardiospasm by cutting the vagi to the lower esophagus Then he was able to overcome the condition by destroying the sympathetic supply through removal of the celiac ganglion His work frequently is cited now in support of a pathological disturbance of the autonomic nervous system However Cannon did not observe the same results in dogs and Vinson Craig and Moersch[31] report a case in which a cervicothoracic sympathetic ganglionectomy failed to relieve the condition For these and other reasons it has been suggested that the changes in Auerbach's plexus follow the dilation and stagnation of food rather than serve as a cause

Recently Etzel[3] has reported that the disease occurs with great frequency among the poor country people of Brazil Because of their limited dietary he believes an inadequate supply of vitamin B_1 may be responsible for the degenerative changes in the intramural portion of the autonomic nervous system Intensive therapy with the vitamin B complex has failed to relieve the condition in my patients and if vitamin deficiency is responsible for the nervous disorder the changes appear to be irreversible

Disease elsewhere has long been considered a cause of idiopathic dilatation which may be encountered in diseases of the upper abdominal viscera such as duodenal ulcer etc In the writer's series the association has been no greater than can be explained through coincidence The incidence of nervousness is admittedly high in these patients Yet it is still a matter of reasonable skepticism whether nervousness can be the primary cause or simply the trigger mechanism which sets off a more fundamental disorder

The condition occurs more commonly in females than males in the ratio of about 3 to 2 The condition occurs at all ages In our cases it varied from 4 to 68 years with an average of 49 years The majority of patients are seen in the third and fourth decades

Pathology — Dilatation always is present and may be very marked It is not uncommon for the organ to hold a quart of fluid and in extreme cases as much as 2 to 3 quarts Accompanying this is a thinning or thickening of the walls which varies considerably in different cases and in different places As a result of hypertrophy the wall may become 3 to 4

times its normal thickness Varying degrees of esophagitis occur depending upon the duration and the amount of existing stagnation

The histological changes in the autonomic nervous system as already discussed under the etiology have been described frequently enough to make them a part of the pathological picture Pulmonary infection may result from the inhalation of food from an inadequately emptying esophagus

Symptomatology — The more important symptoms are dysphagia local discomfort and regurgitation Difficulty in swallowing develops suddenly and completely for all kinds of food An otherwise normal patient may be unable to continue eating or drinking This of course differs from the patient with carcinoma who first notices an inability to get down solid food The individual usually is aware that the food is not passing into the stomach and on questioning will point to the lower sternum as the point at which the material is being held up After a few minutes or longer the food is felt to pass into the stomach and eating can be resumed Occasionally warm fluids will relieve the obstruction

The duration and completeness of the dysphagic attack varies with different individuals The attacks may be transient and occur at varying intervals of days or weeks or months or they may be fairly continuous Once they have occurred swallowing proves bothersome most of the time until relief is obtained by appropriate therapy

Discomfort is a very variable symptom and probably depends upon the amount of esophagitis and irritability which is present Some patients experience only a sense of fulness which differs considerably in various individuals Others complain of burning cramps or acute pain At times the quality of pain in the early morning hours is such as to suggest a peptic ulceration

Regurgitation is another variable symptom which results from irritation and reverse peristalsis Some patients experience it frequently others are never bothered by it Drooling during sleep sometimes occurs The patient awakens to find the pillow wet with viscid saliva characteristic of the esophagus Although the earlier textbooks stress this as an important symptom nowadays it is encountered rarely

Physical examination rarely reveals anything characteristic but evidence of loss of weight is encountered frequently

Diagnosis — The x ray is the most useful means of diagnosis and reveals a smooth funnel shaped constriction with dilatation proximal to it Dilatation is marked and is greater in relation to the duration of symptoms than one sees with a carcinomatous obstruction The narrowing occurs where the esophagus passes through the diaphragm is flexible and allows the barium to trickle into the stomach depending upon the

position of the diaphragm Ordinarily the barium is held up during in spiration but runs into the stomach as the diaphragm ascends

Although the roentgenological diagnosis usually is quite accurate it cannot be relied upon implicitly in all cases At times carcinoma produces a smooth constriction with moderate dilatation thus making it impossible for the roentgenologist to differentiate between the two Flexibility of the outline with change in shape between inspiration and expiration favors a benign lesion

Esophagoscopic studies are useful in ruling out other conditions such as carcinoma peptic ulcer foreign bodies etc and in determining the amount of esophagitis which is present Varying degrees of redness bleeding points and small ulcers may be seen depending upon the amount of esophagitis The cardia itself appears normal and permits easy passage of the instrument

Usually the diagnosis is made without difficulty from the symptoms which suggest a spasmodic obstruction and a characteristic x ray appearance However many patients do not exhibit all of the characteristic criteria of a typically sudden onset spasmodic symptoms and x ray findings At the Peter Bent Brigham Hospital only 41 per cent had a typical onset and 35 per cent typical symptoms The x ray was characteristic in 73 per cent

The most common error is to mistake carcinoma for idiopathic dilatation a point which has been discussed already under the former disease Fewer mistakes will be made if the clinicians will remember two facts (1) The insinuation of a gradually increasing obstruction against the background of spasmodic symptoms always favors a carcinoma (2) The amount of dilatation relative to the duration of symptoms always is greater with idiopathic dilatation than with any other cause of esophageal obstruction

There may be difficulty in distinguishing between idiopathic dilatation and simple spasm at the cardia Generally speaking simple spasm is more transient is not as severe and causes less dilatation Not infre quently diffuse spasm is confused with idiopathic dilatation This error will not be made if the physician discriminates between the roentgenolog ical picture of spasm and dilatation

Treatment — Overdistention of the cardia still is the best form of treatment This is carried out most efficaciously by introducing into the cardia a rubber bag which can be inflated Since Russell's[33] description of this therapy in 1898 numerous modifications of the original apparatus have been devised and can be obtained from any of the larger instrument companies

The procedure is not difficult if the following rules are heeded To insure passage into the cardia and to guard against a penetration of the esophagus the instrument should be guided by a previously swallowed silk thread These bags are made with a diameter of about two inches on the average are ordinarily distended with a pressure of around 300 millimeters of mercury if air is used or a somewhat higher pressure if water is the dilating substance The results with such an apparatus are satisfactory for the most part although duration of relief varies with different patients One satisfactory dilatation will produce a permanent cure with some although in others recurrence may develop within a few months to several years Some individuals need several dilatations from 3 to 10 days apart before satisfactory results are obtained The majority of patients require dilatation *on the average of about once a year*

The operation involves the risk of rupturing the cardia which however happens less frequently than one would anticipate considering the degree to which the organ is stretched Vinson[34] believes that a preliminary dilatation with a 60 French sound may decrease the possibility of a fatality

The use of mechanical spreaders with which the amount of applied force cannot be accurately measured is distinctly contraindicated and should never be attempted They have been responsible for many fatalities in the past

Most patients suffer little discomfort from the bag and the procedure may be carried out without anesthesia Occasionally a patient has a severe reaction with much pain and suggestive symptoms of collapse followed by fever and leucocytosis For these cases it is safer to use the Hurst bougies which are weighted with mercury They come in various sizes of 16 to 64 French are flexible and are easily passed The dilating effect comes from the steady pressure exerted by the weight of the mercury and eliminates the danger of exerting undue force These contribute a valuable addition to our mode of therapy and have decreased the need for using the dilating bag After an original dilatation with the bag many patients can be taught to use these bougies whenever symptoms recur

Ordinarily any esophagitis will disappear after adequate dilatation has been accomplished but any persistence of the trouble can be treated with irrigations of warm normal saline solution

Surgery has been used for immediate relief of patients near death from starvation for those in whom dilatation could not be successfully accomplished for those in whom dilatation proved unsatisfactory and finally in an attempt to cure the underlying disorder through a sympa

thectomy When a gastrostomy is indicated for immediate feeding the cardia may be dilated manually with satisfactory results

Ordinarily instrumental dilatation can be carried out successfully provided a careful effort is made to insure the swallowing of a silk thread and surgery should not be needed merely because of a failure to introduce a dilating instrument

Surgical treatment may be recommended for the intractable cases with marked dilatation Churchill[3] has done several esophagocardio plasties after bouginage has been tried for years and an impasse reached He says my impression is that at least for a period of months very real relief is obtained by the operation I must confess however that I do not understand why My experience has been that even if a large opening is made directly between the esophagus and stomach post operatively the esophagus looks just the same by x ray with a fluid level and dilatation

An attempt to balance the nervous innervation by a sympathectomy has been tried in a few instances Because of the uncertainty as to where the sympathetic innervation arises some surgeons have removed the abdominal ganglia and others have cut the cervical or thoracic fibers with apparently indifferent results

Drugs have a limited value Atropine has a beneficial effect in some instances Occasionally it will produce complete relief in a mild case with incipient symptoms and sometimes it will ameliorate the more severe case This is of interest because according to the current views on etiology atropine should be contraindicated Perhaps the mild cases which obtain benefit are not suffering from true idiopathic dilatation Drugs which cause relaxation of smooth muscle frequently will produce transient relief Benzedrine sulphate in doses of 5 to 10 mgm 2 to 3 times a day can be useful to tide a person over a short interval until dilatation can be performed Sedatives like the bromides are beneficial for the nervously unstable individual

In view of the current literature the B vitamins may be prescribed if there is reason to suspect a deficiency However there is no present proof of their value

Congenital and Morphological Malformations of the Esophagus

Congenital Atresia

Congenital atresia of the esophagus is a rare anomaly only 32 cases having been observed in eleven years at the Children s Hospital in Boston[36]

Knowledge of the embryological development of the respiratory organs helps to understand the types of congenital malformations which can be encountered The lung buds arise from the foregut to form the trachea First a ridge develops on the ventral wall of the foregut Later two lateral longitudinal grooves mark off the dorsal esophagus from the ventral anlages The lateral grooves unite gradually forming a septum which grows cephalad and separates the tracheal tube from the esophagus During this process the following abnormalities may develop (1) Complete absence of the esophagus (2) Complete separation from the trachea with a division remaining between the upper and lower segments of the esophagus This may be complete the two segments being joined only by strands of connective tissue or incomplete with the presence of a web between the two segments The lower of the two segments also may end blindly (3) The upper segment communicates with the trachea and the lower one with the stomach (4) Both the upper and lower segments have a communication with the trachea The commonest anomaly is a blind upper segment with the lower one communicating with the trachea

Symptoms — Choking and cyanosis develop in the first hours of life These symptoms are aggravated by the taking of liquids which are apt to be regurgitated immediately The regurgitated material often is frothy Abdominal distention occurs from the aspiration of air when the lower segment communicates with the trachea and is normally joined to the stomach

When partial stenosis of the esophagus is present symptoms may develop only after the child starts to take solid food However if the constriction is quite marked regurgitation may follow the rapid ingestion of liquids

Diagnosis — If there is reason to suspect an atresia the patient should not be given barium the inhalation of which is always followed by pneumonia The use of iodized poppy seed oil also is unwise The safest procedure is to pass a soft rubber catheter as far as it will go and then take an x ray This will reveal the level of the upper pouch If no gas is present in the stomach or bowel the lower pouch is blind and the upper one may be If the catheter meets obstruction and gas is present in the stomach and bowel there is a communication between the lower pouch and the trachea

This procedure gives all the information which the physician needs to know about the esophagus However these patients should be examined carefully for other serious malformations Many show an imperforate anus atresia of the ileum and duodenum rectovesical fistula or Meckel s diverticulum Various other abnormalities have been reported less often

Treatment — Surgery is of course, the only hope for the patients with blind pouches This is still in an experimental stage, and surgeons are trying approaches through the posterior mediastinum and by the transpleural route Lanman[6] reported fatalities in all of the 30 cases operated upon in his series

The treatment for those patients with a partial constriction of the esophagus is dilatation Usually this can be deferred until the child is ready to start on solid food and may wait until he has reached the age of one or two years The technique is the same as for any stricture and usually one or two dilatations is sufficient

Congenitally Short Esophagus

Congenitally short esophagus is a condition in which the esophagus fails to grow to its full length so that at least a part of the stomach remains a thoracic organ Although not many cases have been reported it is probably more common than has been supposed, its recognition depending upon the frequency and care with which patients are x rayed

The symptoms are similar to those of a diaphragmatic hiatus from any cause, such as trauma congenital weakness of the diaphragm or failure of the diaphragmatic leaves to close completely The symptoms are numerous any combination of which may be elicited from individual patients They consist of epigastric distress pain along the costal margin in the back axillæ subscapular and shoulder regions Pain may be experienced even in the arm and hand Patients may complain of heartburn dysphagia palpitation, dyspnea and cough

The symptoms appear to arise locally from a gastritis and a pressure on the mediastinal organs The distant pains and aches can be explained best from irritation of the nerves involving the diaphragm and lower mediastinum

Epigastric distress occurs in about two thirds of the cases and is encountered with both small and larger herniæ It may be particularly troublesome at night Pain along the costal margin is not so common and may be experienced on either side Heartburn occurs particularly with small herniæ Regurgitation and vomiting are frequent symptoms and one may exist without the other Vomiting is encountered more often with the larger herniæ Bleeding is fairly common and all degrees from oozing to massive hemorrhages are encountered A diaphragmatic hernia is one cause of an otherwise unexplained anemia Dyspnea and borborygmus are more prone to occur when much of the stomach is in the chest When a patient is lying down smaller herniæ produce a

combination of heartburn and upper epigastric or substernal pressure which causes the individual to seek an upright position

Cases can simulate closely an angina with their substernal distress and pains in the shoulders and arms A differential diagnosis can be difficult because cases are reported in which the symptoms may follow exertion or eating and be relieved with nitroglycerine The similarity is at times so close as to suggest that perhaps an angina may in fact be stimulated by a reflex effect on the coronaries The distinguishing point between angina and a diaphragmatic hiatus is that the anginal like symptoms are more variable than in true heart disease Careful observation shows that these symptoms are not invariably brought on by exercise and the relief from nitroglycerine is not so definite The patients are more prone to have right sided pain than is the case with true angina Nocturnal attacks are common with herniae and the patient wishes to move around whereas night attacks are not characteristic of angina and when they do occur the patient prefers to remain quiet

The radiation of pain to the shoulder and subscapular area may raise the possibility of gallbladder disease At times the epigastric distress may simulate closely a peptic ulcer

Diagnosis — When the greater part or all of the stomach is in the chest the condition may be diagnosed by a careful physical examination Unusual thoracic tympany which may disappear upon eating the presence of thoracic borborygmi and the displacement of the heart are valuable signs

Small herniae can be diagnosed definitely only with the aid of the x ray A small herniation can be missed easily and the clinician should not accept one negative report as eliminating the possibility of a hernia If the roentgenologist finds a hernia the clinician wants to know whether he is dealing with a congenitally short esophagus The length of the esophagus may be determined by passing a stomach tube to a distance of 16 inches from the incisor teeth and locating radiographically the relation of the tip to the cardia

Treatment — Most cases with lesser degrees of herniation should be treated medically Surgery is difficult and the results are not very satisfactory It is virtually impossible for surgery to do anything for the congenitally short esophagus The medical treatment includes a bland diet and the use of antacids Atropine will benefit some of these patients and should be given to physiological tolerance The patient should be advised to eat slowly Maintaining the upright position for one to two hours after eating is a prophylactic measure and it is well to advise a semi reclining position during sleep

Diverticula of the Esophagus

In 1764 Ludlow[7] described the esophageal pockets which he had observed at autopsy In 1816 Bell[38] recognized the pharyngeal diverticulum as a herniation of the mucosal elements through the pharyngeal muscle and recommended the establishment of a fistula to drain its contents In 1877 Zenker and Von Ziemssen[39] were the first to classify the diverticula into the pulsion and traction types

Diverticula are common and arise at any level of the esophagus They represent 2 5 per cent of all esophageal abnormalities observed in the x ray department of the Peter Bent Brigham Hospital Two types of pouch occur The so called pulsion diverticulum develops from the intra esophageal pressure established during swallowing The other the traction diverticulum as its name implies, results from traction on the esophagus if the latter becomes adherent to a neighboring structure Pulsion diverticula are true herniations of the mucosa and submucosa through the muscular layers They develop in the pharynx just above the esophageal opening and in the distal portion of the organ above the diaphragm Traction diverticula are a bulging of the intact walls which contain all the layers of the esophagus These are seen most often at the tracheal bifurcation where the mediastinal lymph nodes are prone to become inflamed

Pharyngeal diverticula most often cause symptoms and rarely the ones just above the diaphragm may become troublesome Those in the mid esophagus are almost always of the traction type and rarely give trouble

Pharyngo esophageal Diverticula —Symptoms begin to plague the patient when the mucosal structures first begin to force through the muscular layers There is a sensation of food sticking in the throat and the patient coughs frequently in the endeavor to rid himself of the trouble As the process progresses a sac develops along the left side of the esophagus and has a definite neck At this point food mucus and air accumulate in the sac and produce gurgling As these can be heard easily by others they are a source of considerable embarrassment for which the patient frequently consults his physician Also at this stage the individual begins to regurgitate food which he recognizes as having been eaten at some previous meal

As the sac enlarges the weight of the retained food pulls toward the mediastinum and exerts a definite drag on the pharynx[40] This pull tends to rotate and angulate the esophagus in such a way as to bring the opening of the diverticulum into the line of direction which the food is

taking At the same time it tends to move the normal opening of the esophagus to one side and close its lumen which as now viewed through the esophagoscope assumes *the appearance of a longitudinal slit in a* lateral position Now the patient finds that during a meal swallowing becomes increasingly difficult and finally impossible Most patients learn to empty the sac by an upward stroking motion on the left of the neck after which eating may be resumed After the diverticulum is well developed the diagnosis can be made on the history and physical examination alone Watching the patient eat will demonstrate the characteristic development of difficulty in swallowing Close inspection may reveal a fulness in the left side of the neck which can be overcome with pressure

After a few swallows of barium the x ray will reveal the characteristic pocket in the cervical region The x ray may not help in the early stage when the individual complains only of food sticking in the throat At this time a careful inspection of the pharynx through an esophagoscope should be used to confirm the suspected diagnosis

Treatment — Treatment is of little avail in the early stages Gentle dilatation of the opening sometimes relieves the symptoms but does not prevent the development of the pouch Surgery is the method of choice for the later stages Irrigation of the pouch with a rubber catheter is not without danger and merely decreases inflammation through the prevention of fermentation

The operation consists of a careful dissection of the sac which is then carried upward and fastened to the sternohyoid muscle Under these conditions food can no longer enter the pouch and this procedure alone may relieve patients satisfactorily However modern surgeons advise obliteration of the sac with a second operation At the end of 8 to 10 days the wound is reopened the tip of the sac is snipped off and the mucosa separated from the submucosa The mucosa is cut off at the neck of the sac The remaining tube of submucosa *is packed with* gauze which is withdrawn after 4 to 5 days Using this technique recurrences appear to be infrequent

Traction Diverticula of the Esophagus — The great majority of traction diverticula are symptomless By the time they are discovered the original inflammatory process which caused their formation has subsided and because the pocket is wide open there is virtually no stagnation of food to set up an esophagitis Clinicians should guard against attributing to them functional and vague gastrointestinal symptoms for which no cause has hitherto been discovered Very rarely one of these perforates causing an infection of the lung or mediastinum The symptoms are those of an infection within the chest One case of the writer s de

veloped a fatal hemorrhage from the base of a traction diverticulum, but again this is a very rare occurrence The diagnosis can always be made by the x ray findings

Pulsion Diverticula in the Distal Esophagus — These are extremely rare and usually give symptoms only if they have acquired much size Local sensations of pressure may develop together with symptoms from the decomposition of food within the cavity Regurgitation of this material is very unpleasant and may bring on nausea Furthermore, regurgitation may awaken the patient at night If the diverticulum is small and virtually symptomless no treatment need be undertaken The large ones can be reached by the transpleural route the sac dissected away from the esophagus to which it is usually adherent and the tip fixed to the pleural gutter beside the vertebral bodies In this way the sac is kept inverted and prevents the entrance of food while the patient is in the upright position

Cysts of the Esophagus

Cysts of the esophagus have the same cause as cysts found elsewhere along the gastrointestinal tract Presumably they develop from the diverticula observed in the fetal alimenteric canal These knoblike out pockets of the intestinal wall normally regress but the pinching off of one of these structures may separate it from the normal canal They possess a muscular coat and are lined with epithelium similar to that found in some portion of the gastrointestinal tract but not necessarily the esophagus They may or may not communicate with the esophagus

Ladd and Gross[41] report three cases occurring in the esophagus out of a series of 18 cases of cysts found somewhere along the gastrointestinal tract

Symptoms result from the mechanical effects produced by enlargement of the sac Esophageal compression leads to dysphagia and dyspnea accompanies interference with expansion of the lungs

The roentgenographic findings are characteristic of mediastinal neo plasms or cysts The density of the shadows are rather uniform because of their fluid content These cysts may push the mediastinum and heart to the other side of the thorax

Surgery is the only means of relieving the condition Either one of two methods may be employed Excision may be attempted but the danger of opening the esophagus during the procedure is a real hazard as it usually results in a fatal mediastinitis or pleuritis A more conser vative method is to marsupialize the cyst through a posterior or postero lateral incision and later destroy the lining with necrobiotic solutions

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CHAPTER II

DISEASES OF THE STOMACH EXCEPT PEPTIC ULCER*

By WALTER C. ALVAREZ

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she never coughed If the assistant had questioned her more carefully he would have found that what happened was that she regurgitated a glary white fluid She did not know where it came from An injection of radiopaque oil into the bronchi showed that there was no bronchiectasis and a barium meal showed that she had a diaphragmatic hernia with considerable obstruction at the cardia The material that was running back into her pharynx was saliva coming from a dilated esophagus

Often today patients come in scared to death with the diagnosis of coronary thrombosis and angina They tell a story of thoracic pain but when a good heart specialist sits down and cross questions them as to every detail, it soon becomes apparent that they do not have any heart disease Their pain has no relation to exertion or anger and they can walk rapidly without distress, so evidently their cardiac reserve is good and their pain usually proves to be due to fibrositis in the thoracic wall

One of the best cases with which to illustrate the tremendous need for cross questioning many patients was that of a stout woman whose story as it had been put down by three different assistants appeared at first glance to be that of stones in the common duct Four years before after suffering from several gallstone colics" she had been operated on and a gallbladder full of stones had been removed Following this she went on having the same old colics" every two or three weeks Occasionally with a spell she had a chill some fever and a little jaundice Because this story was so typical of a stone in the common duct the physician was about to send the woman to a hospital for operation but then he decided to follow his rule and cross question her Then to his astonishment he found that she had never had a bit of pain, even before the operation What she had had were spells of vomiting with unilateral headache, in other words attacks of migraine Careful questioning then showed that the gallstones had never given her any trouble and so naturally their removal had done her no good She had had only one chill and that had evidently been a nervous one following a quarrel with her husband and the stories of fever and jaundice did not stand up under cross questioning It was helpful to learn that morphine had never stopped her attacks but injections of gynergen had done so

Evidently the three assistants able young men who one after the other had taken her history had all jumped to the conclusion that any violent attack in a woman who had gallstones must be a colic They did not go into the history in enough detail to find out that there never was any pain Probably the last two had accepted the history taken by the first one Their chief was most grateful that he had not sent the

The Significance of Symptoms and the Value of a Good History in Making the Diagnosis of a Digestive or Abdominal Distress

Many of the histories taken today are too brief for purposes of diagnosis or treatment and often because of this briefness, they are misleading. In many cases if the physician had only asked one or two more questions he could easily have saved himself from making a costly blunder. For instance in a case of cancer of the rectum, diagnosed as duodenal ulcer, if the physician had only asked the patient what he meant by pain in his "stomach" he would have learned that the distress was in the pelvis, and if after the roentgenologist had reported a duodenal ulcer the physician had only asked "when did you have hunger pain"? he would have learned that that was thirty years before, during World War I.

The abler a physician is in any field of diagnosis, the more carefully does he go into the details of every history and the more carefully does he cross question the patient. Often the history has to be taken several times or by several different men before all the important details are clear. Sometimes the vagaries of patients during history giving are hard to explain. For instance a woman came with a roentgenological diagnosis of duodenal ulcer and a hemoglobin reading of 50 per cent. There was no history of hematemesis or black stools. It did not seem probable that blood vessels in a small ulcer could ooze enough to produce such an anemia. The first consultant who saw the woman asked her if she had noticed bleeding from any body orifice or if she had menstruated excessively and she replied "no." The next physician who questioned her, obtained the admission that at times she menstruated for two days rather heavily, the gynecologist who next was called, got the story that she menstruated for two weeks and flooded part of that time. A myomatous uterus proved to be the main cause of her trouble, the duodenal ulcer was unimportant.

Often even a consultant will accept too carelessly the history obtained by an assistant. To illustrate, one day an assistant wrote in the record that a woman was coughing up in each twenty four hours a cupful of sputum. When the roentgenologist reported shadows in the right lung suggesting the presence of bronchiectasis the diagnosis apparently had been made. It seemed so logical that the chief accepted it, but when the lung specialist arrived he promptly brought out the fact that the woman had not said that she coughed up the material. Actually

one day an internist was sending home with a diagnosis of psychoneurosis a man whose problem for six weeks had baffled a number of able clinicians The patient was a lovable Irishman who admitted on entrance that he was so neurotic and at times psychopathic that his epigastric pain might well be due to his stormy emotions, but he was ill and unable to carry on his work and hence he was sent into a hospital for a most careful going over and observation When he came back, after being seen by many specialists and examined in every way his record was half an inch thick Reading over the long complicated story one of the consultants picked out the only three really important facts, (1) that years before the man had had spells of hunger pain (2) that one day he had doubled up with epigastric pain so severe that he had to have morphine and (3) that following this his pain had been relieved only occasionally by the taking of food and alkalies The logical diagnosis then was that of a duodenal ulcer that had penetrated into the head of the pancreas and when the man's abdomen was explored that is exactly what was found The operation cured his pain and restored the man to work but of course it did not clear up the psychoneurosis

Detailed History Necessary not Only for Diagnosis but for Treatment

Often in a few minutes an able physician can be sure that the nervous woman sitting in front of his desk has a decided neurosis and that her troubles probably are all functional but before he can go ahead and treat her intelligently and successfully he will have to spend perhaps an hour drawing out the long story of such things as overwork strain sorrow unhappiness marital infelicity or psychopathic thinking which may have worn her down Then he has to learn enough about her and her life and economic situation to know what he and she can do in the way of treatment

In another case it may be obvious in a few minutes that the woman has a severe migraine but again the physician will have to talk to her for a long time to find out why she is having her attacks so frequently and what can be done to help her stop them from coming

Need for Questioning Relatives and Friends

Often the really important part of a history the part that is essential to the making of a diagnosis can be obtained only from a relative a business associate or the family physician This is particularly true in the case of those patients who are psychopathic or psychoneurotic who

woman in for a futile operation and he decided that in the future, more than ever before he would fight his constant temptation, when in a hurry to put down broad statements that had not been clarified or made definite by careful cross questioning In another similar case, in which the story was that a stout woman with a nonfunctioning gallbladder was having colics careful questioning brought out the fact that what she was having were really hysterical spells due to sprees of heavy drinking When she stopped drinking and her liver function became normal again her gallbladder filled well with the dye

Need for Seeing the Patient at Intervals During an Examination

As a patient is being put through a complete examination, it is a good thing to have him report every day or two for a few minutes to see what evidence has turned up There are at least two reasons for doing this The first is that as reports come in the plan of campaign may have to be altered Let us say that a man with what was supposed to be gallstone colics is found next day to have red blood cells in his urine This means that the urinary tract must be studied by a specialist, and it should be done before any barium is put into the digestive tract Another reason for watching from time to time is that if the diagnosis should happen to be made in the first day or two it might then be foolish to go on with the rest of the examination To illustrate an old man came in with a story of (1) a cough (2) some attacks of fainting and vertigo, (3) some arthritis and (4) some difficulty in urinating The able young assistant who started him out gave him orders for more than $100 worth of tests and roentgenological and special studies all intended to throw light on these four troubles He told him to return in ten days or two weeks whenever the advised studies had been completed The chief happening to come into the room suggested that the man return the next day when the roentgenological report of the lung would be in This showed an inoperable carcinoma of the bronchi the neurologist agreed with the chief's hunch that there was metastasis to the brain, and under these circumstances there was no need for putting the man through the rest of the examination

Ability to Disregard "Red Herrings" Drawn Across the Diagnostic Trail

Oftentimes the skill and experience of a trained consultant show up best when out of a voluminous and puzzling history he picks out the few essential items and from them makes the correct diagnosis To illustrate,

the patient's statement that he has stomach or heart trouble or vomiting or diarrhea or what not Let us say that a man who is suffering with a fibrositic ache around the left costal margin a very common disease goes to a gastroenterologist and says he has pain in his stomach The assistant, who takes the history is almost certain then to write patient has pain in his *stomach*", and then to send the man for a gastric analysis and a roentgenological study of his digestive tract If some days later when the man returns and sees the consultant for a few minutes for his final summing up his reports should state that he has hyperacidity and an irritable duodenum Then he is likely to be sent to the hospital for a Sippy treatment If that does not help him he is likely to get another Sippy treatment But if instead of this, the patient had gone to a heart specialist and had said that he had pain in his heart the assistant probably would have sent him for an electrocardiogram and if this had shown a few slurrings and notchings he might have gone home with a diagnosis of myocarditis a prescription for digitalis and the injunction to walk slowly

When the patient says he is vomiting the assistant should not just put this down and let it go at that but should ask what is meant by vomiting Are a few mouthfuls of food coming up right after the meal, or even during it without nausea or does the patient suffer for hours and then bring up a liter or two of undigested food or does he vomit only bile stained water for a day or two? The first syndrome is due to a neurosis the second probably is due to a pyloric lesion and the third may be due to migraine Similarly if a woman says she is having diarrhea , she may not be having diarrhea at all She may be so frightened over the illness of a child or an impending divorce that she is running to the toilet every half hour to pass a *tablespoonful* of watery mucus with some gas What she is having is a nervous storm in her colon

The physician always must make sure that he understands correctly what the patient means by certain words For instance it is tremendously important to know that when the patient says pain he does not really mean this but rather a sense of burning quivering pressure throbbing tension or aching Burnings and quiverings are practically always functional in origin Burning usually is a paresthesia in the skin Heartburn in most cases appears to be a functional trouble

One of the most important things that a gastroenterologist can do is to find out what a person means when he says stomach Often he means his abdomen and because of this common mistake he must be made to point exactly to the place where the distress is felt It may be

are going insane who have had a little stroke or an attack of encephalitis or who are getting their first symptoms of a brain tumor They are not likely to speak of the all important changes in character and loss of efficiency, judgment and drive Often the family knows all to well that the patient is changed and is a terrible problem at home, but they fail to mention such facts because they think he is just cussed, and if he could get over his stomach trouble he would snap out of his moodiness and go back to work

Often the only way in which the observant physician can get tipped off to the need for asking questions of the family or of business associates is by a glance at the patient s occupation as listed on the master sheet of the history Often then it will be obvious that the seedy-looking mentally slowed up man sitting in front of the desk could not possibly be the president of a large department store or production manager for a big automobile company or manager of a big hotel Evidently something must have changed him and greatly injured his brain Most young physicians today have not been taught to observe these things and to realize their tremendous significance in making the diagnosis

To show how helpful such observations can be a man of fifty complained of digestive troubles and distress in the abdomen An able young assistant put him through the usual diagnostic mill and decided that he had an ulcer His chief noted right off that the occupation listed was boiler maker s apprentice and asked how it happened that at fifty he hadn t yet been promoted The man answered that he really was not a boiler maker's apprentice but was given that title only so that his son could use him a little around the roundhouse of a railroad Actually until three years before he had been a farmer and a fine successful one Then one day during an epidemic of equine encephalitis and while nursing three sick horses he had collapsed, after that he had been somnolent for several weeks and finally had come out of the illness with so badly crippled a brain that he could not take care of his farm He was a wreck but that did not show up in any of his tests

Many a time if a physician would only suspect the presence of a psychoneurosis and then question the relatives and friends and business associates, he would get a story that would astonish him

Danger of Accepting Unquestioningly the Diagnosis With Which the Patient Comes

One of the worst features of a hurried or mechanized practice of medicine is the physician s willingness often to accept unquestioningly

of the colon The physician who has already made his diagnosis of migraine or an epileptic equivalent, is not likely to be stampeded by these reports and led astray by them

In the last twenty years or more in medical schools there has been an unfortunate tendency to show the students all the rare and bizarre cases that turn up As a result the graduates come out into practice without any ability to recognize the common neuroses and functional disorders which throughout life they are going to see every day Often it does not even occur to them when they meet some of these disorders that they are functional in nature

What Is the Principal or Most Troublesome Complaint?

In starting to take a history it is a good plan to try to make certain what is the patient s most troublesome complaint What does he feel is his most important trouble or the one that he would like most to get rid of The fact that a patient does not know how to answer this can immediately tell the physician a lot about his trouble Many patients will answer oh I have so many troubles all over that I do not know where to begin', and that practically makes the diagnosis. In many cases when a woman comes in she may complain first of a pain in the abdomen but later she may say that the really troublesome symptom is a toxic feeling in her head On another day she may say that what bothers her most is her backache another day it is her sick headache and another day it is her great feeling of fatigue

Often the experienced physician will make the diagnosis of a functional trouble the minute the woman comes in with a long list of symptoms written out or even a small book filled with notes

How Long Has the Trouble Been Present?

Naturally it is often very helpful to learn that a pain or distress has been present for years because obviously then it cannot be due to a cancer or other serious disease In many cases of abdominal pain it is helpful to remember that tumors growing in the small bowel or narrow left half of the colon are almost certain to obstruct within six months after they begin to produce symptoms. Often the surest way of cheering the patient is to remind him that he can hardly have a cancer because he has had the same symptoms for too long a time

anywhere from the tip of the sternum to the region above the pubes, it may even be down in the pelvis

Another important word the meaning of which must be ascertained by cross questioning is gas By this the patient often means repeated belching which is due to the swallowing of air This is due usually to fright over something or just jitteriness or a psychoneurosis Sometimes by gas the patient means bloating but even then the physician must differentiate bloatings of various kinds some due to indigestion, some due to nervousness and some due to the drinking of a glass of cold water Sometimes by gas the patient means that he is having more than the normal amount of flatus but even then he must be questioned as to details Flatus that is due purely to swallowed air usually is odorless

A patient often says he has had a tarry stool, but this usually does not mean much if he was not weakened by it, or if at the time, he was taking bismuth or eating beets or Concord grapes Every year an internist will see many patients who have been through one diagnostic mill after another because of so called fever' Actually they did not have fever but only a temperature of 99 4 F when they were nervous and worried

The wisdom of a physician can be judged by the skill with which he takes a history and the way in which he pounces on one clue after another and follows it out to its logical end For instance a woman may say that she has frequency of urination A young assistant may want immediately to send her for a culture of the urine and examination by a urologist but his chief may draw out the facts quickly (1) that she goes to the toilet every twenty minutes during the day (2) that she has no trouble at night and (3) that she is worried sick over something From these facts he can safely make the diagnosis of a nervous bladder

Advantage of Making a Diagnosis From the History

Today, when so many little abnormalities turn up during the general examination, the laboratory tests, the roentgenological studies and the special examinations it is extremely important that in many cases the clinician make the diagnosis of a functional trouble or of some organic disease from the history When he has done this, he is not so likely to be led astray by some unimportant or insignificant finding

Often today physicians think that they can make the diagnosis of a neurosis by exclusion but it is dangerous to depend on this because too often the roentgenologist reports a deformed duodenal cap a slowly emptying gallbladder, a peculiar looking appendix or some diverticulosis

it is out here in my skin' That statement alone may save him from a fruitless operation

How Did the Pain Come?—The physician often can learn a great deal by finding out how the pain first came What was the patient doing? Was there, at the time, great worry fatigue or excitement, a family argument or a tantrum of temper Was the patient traveling eating poor food did he have a bad cold or had he been feeling poorly for a while? Did a physician see the patient in the first spell and what did he think about it Did he have to give morphine, and did he want to perform an operation?

Is the Pain Coming in Attacks or Is It Constant?—Pain that comes in attacks is somewhat more likely to be organic in origin while pain that is steady or present day after day or year after year is more likely to be psychogenic Often such pain turns out to be only a dull ache Perhaps the patient admits he would not complain about it if he were sure what it was due to and that it would not turn into anything'

Pains which come in attacks perhaps at first a year apart then six months apart and finally at shorter intervals until they get to coming every day usually are functional in nature, or at least no organic cause can be found for them in the abdomen

Does the Pain Shift About?—Pains that shift about a great deal and out of the thorax or abdomen are not so alarming as those that stay in one place

Length of the Attacks and the Intervals Between—The wise clinician often can learn something about the cause of a pain by noting the length of time during which an attack lasts and the length of the interval between attacks For instance, pain due to angina generally lasts only a few minutes and goes away as soon as the patient rests Pain due to gallstones is likely to be relieved soon after the patient gets a hypodermic injection of morphine Pain due to ureteral colic may last longer and the patient may need several large doses of morphine A stormy attack of vomiting due to migraine may come several times a month and last for two or three days Attacks of gallstone colic may come at intervals of months or years Attacks of pain due to peptic ulcer are likely to come twice a year in the spring and the fall Pain around the liver due to hepatitis may last for weeks or months.

The Exact Location of a Pain Is Important—As already pointed out it is highly important to have the patient strip and show with his hand exactly where the pain comes and how it radiates.

One very useful point not well enough known to physicians, is

Naturally the physician must be greatly concerned over a short history of any kind in a person past middle age who previously has enjoyed good health It always suggests the coming of some serious illness The physician then should examine the patient most carefully in an effort either to find serious disease or else to rule it out When a previously healthy oldster falls ill the wise physician will not be content to diagnose diseases of youth such as mucous colitis, food allergy, appendicitis or nerves, but will go hunting for serious organic disease

Importance of Getting Details as to the Beginning of the Disease

Oftentimes as in puzzling cases of old ulcer, the only way in which the diagnosis can be made is through getting the story of the beginnings of the trouble Often the early attacks were typical of ulcer but later after the coming of some penetration into the pancreas or some pyloric obstruction the history became confused and the syndrome atypical

In many cases it helps to learn that the first attack came with some manifestations of hysteria and at a time when the patient was under great psychic stress This will suggest that the recent attacks, which look like those of organic disease, are still of functional origin In some cases of vague indigestion the trouble can be traced back to an attack of diarrhea due, perhaps to the eating of infected food

When older persons come in with symptoms suggesting injury to the brain, it is well to trace the story back to its beginning because sometimes one can get the history of a typical small stroke or an attack of encephalitis Often when a person fears that he or she has heart disease it helps greatly to go back and get the story of the first attack and the conditions surrounding that event Often then it will be obvious that the whole thing started with a fright and has been kept up by fear

Abdominal Pain

Is the Patient's Trouble Really Pain?—As already pointed out, often the most important point diagnostically is to find out if the patient's complaint really is pain, or if it is something else perhaps a symptom which is known always to be associated with functional disease

Is the Pain in the Abdominal Wall or Deep in?—Sometimes if the patient is asked if his pain is deep in the abdomen he will say, "why no,

because some physicians give morphine on little more than a suspicion of pain

One can get some idea of the severity of a constant ache by finding out if the person is able to work with it or to get sleep fairly easily Often a pain is worse at night because then the patient has nothing to distract his mind from it Pain that so frightens the patient that he or she does not dare to eat generally is due to organic disease often in a stout woman it is due to cholecystitis

Oftentimes it would be helpful to find out how sensitive or insensitive a patient is so as to know if he was complaining too much or too little Something can be learned by noting how much of a fuss is made when let us say, a sigmoidoscope or a stomach tube is passed or by asking how the dentist's drill is tolerated

Soreness After Pain —Strongly suggestive of an organic cause for pain is localized soreness after an attack Suggestive also of a local inflammatory process is pain which is felt on jolting in an automobile or a tractor

Is There More Than One Pain?—Often it is essential that the physician learn that the patient has more than one pain For instance, a woman who suffered from angina pectoris, also had both a diaphragmatic hernia with a third of the stomach in the thorax and gall stones It was an interesting puzzle to try to unscramble her history and to assign her different distresses to the several lesions Interestingly all of her distress cleared up for a time when she was made to take off some 30 pounds of fat (13 6 kg) localized largely in the abdomen

Characteristics of Pain —It may be helpful to learn something of the characteristics of a pain, whether it is steady throbbing or burning or more of an ache A pain that comes at short intervals, like a labor pain will suggest that there is some intestinal obstruction with strong peristaltic contractions of the bowel Colicky pains are likely to be arising in the bowel or in the ureter or perhaps the bile ducts Often a patient will say that the pain appears to be due to gas somewhere, and he will have the strong impression that, if only he could pass the gas or have a bowel movement he would be relieved Probably he is right Even the pain of peptic ulcer often feels like a gas pressure The pain of gallstone colic may interfere with breathing or it may feel as if something were being distended in the lower part of the thorax With heartburn there may be a sense of distention or rending under the sternum The pains that are due to fibrositis in the thoracic or abdominal wall may have

the fact that pain arising in the stomach, gallbladder, liver or duodenum is likely to be felt above the navel Pain felt below the navel is likely to be originating in the colon or the pelvic organs Many a wrong diagnosis is made because the physician ignores this rule Pains arising in the kidneys or urinary tract are likely to be felt in the flanks and to run down along the ureter toward the testicles and penis In thousands of women pain and soreness follow the course of a sore colon In a few they coincide with a tender aorta

A shift of the location of pain in cases of gastric ulcer or carcinoma may be due to penetration of the lesion through to the peritoneal coat where a different set of nerves becomes involved After gastroenterostomy or partial gastrectomy a return of the pain with a shift to the left and below the navel strongly suggests the coming of a jejunal ulcer

Pain arising in the pancreas is often felt in the middle back, the left hypochondrium or the lower part of the thorax It tends early to demoralize the patient Helpful in the diagnosis is the point that the patient is seldom able to work or to keep out of the hospital very long after such pain starts

Pain arising in a diaphragmatic hernia often will imitate that of heart disease or cholecystitis It may extend up into the thorax As is the case with cholecystitis, it is likely to be better if the patient eats little and avoids large meals It may be better if the patient sits up in bed

As is well known, the pain of gallstone colic is likely to extend under the right scapula The pain of acute appendicitis is likely to be felt first around the navel the place of reference for the ileum, and then to shift to the right lower quadrant of the abdomen when peritonitis involves nerves which go out through the flank Pain and soreness in the groins which comes on standing is likely to be due to a knuckle of bowel boring into a large internal inguinal ring

Severity of the Pain—Much often can be learned about the nature of a pain from its severity Pain in the upper part of the abdomen requiring hypodermic injections of morphine is due most commonly to gallbladder colic It is rarely due to ulcer unless this has penetrated or perforated It may be due to a stone in a kidney or to disease in the pancreas Rarely it is due to a diaphragmatic hernia or to pneumonia involving the right leaf of the diaphragm Occasionally it is due to coronary disease or to thrombosis of a little vessel in the brain with reference of the distress out into the thorax

However, before judging of the severity of pain from the fact that morphine had been given one should know about the patient s physician

pains always come after the eating of a certain food to which the patient is sensitive Pains arising in the pelvic organs of women are likely to flare up during the menstrual period

What Lessens a Pain or Stops It? — Something can be learned about a pain by finding out what will help to make it stop Ulcer pain of course is relieved commonly by the taking of food or alkalies by belching by vomiting or by getting the stomach washed out Some abdominal pains as in the case of carcinoma of the stomach can be lessened by fasting

The pain of angina pectoris can be stopped by resting, by standing still *or by taking some nitroglycerin* The pain due to arthritis of the spine can be helped or relieved by a little exercise The pain of migraine can be stopped by taking a hypodermic injection of gynergen (ergotamine tartrate) In many cases the pain of a gallstone or ureteral colic will not stop until morphine is given

Pain in the epigastrium relieved by sitting up, may be due to heartburn, diaphragmatic hernia heart disease or pancreatitis The man with terrible pain due to cancer of the pancreas may have to sit up much of the night bent over forward with the arms around the knees Pain arising in the colon may be relieved by the taking of an enema

Is the Pain Originating in the Digestive Tract? — When a patient has abdominal pain, one of the most important things the physician can do is to ask a few questions which will show whether the source of the trouble is in the digestive tract Just the knowledge that it is not there may save the patient from a useless laparotomy The pain is not likely to be arising in the digestive tract, if it is not influenced by the taking of food or the emptying of the bowel by taking alkalies belching vomiting passing flatus or taking a laxative or an enema *Often if a patient* with abdominal distress is questioned as to his digestion he will say that he has a cast iron stomach and can eat anything and digest it with comfort He may go on to say that eating has nothing to do with his pain It is sad to think that today so few physicians use this extremely important diagnostic technic

Pain which comes immediately after eating is not likely to be due to ulcer and can hardly be due to food allergy or to indigestion the food has not been in the stomach long enough to exert any specific effect Often in such case all one has to do is to ask the patient if a drink of ice water will produce the same distress and he will say "yes" Evidently then the symptom is produced simply by distending the stomach or by the physical impact of the food or the water Such a stomach would

an element of soreness of the tissues mixed with them Oftentimes there will also be lancinating jabs or long continued aches

The so-called root pains tend to follow the distribution of one or two nerves Pains of cardiac origin should come when the patient is exercising or is under strong emotion and particularly, if he tries to walk after a good sized meal or against a cold wind After a few minutes of rest the distress should go away and allow the man to proceed

Characteristic of a psychoneurotic pain may be the fact that there is some distress along the whole side of the body from the face to the toes Suggestive of such a psychosomatic pain also is the fact that it is present day and night over the course of months or years Localized pains of organic origin are much more likely to come and go

Symptoms Accompanying Pain—Often it can help to find out what symptoms accompany a pain For instance with a gallstone colic there may be nausea, a catch in the breath and later, abdominal soreness and a little jaundice Often the patient, usually a woman, wants to rush home from a luncheon party to tear off her girdle and get relief from her feeling of distention in the abdomen She may be unable to sit with her back against an uncomfortable chair or to sit at a sewing machine

With a renal colic there may be distress running down to the bladder and frequency of urination With the pain of pleurisy there may be cough and fever and distress on taking a breath With pains, which are due to fibrositis or to arthritis around the spine with involvements of nerves, often there will be a story of attacks of lumbago or sciatica or of arthritis here and there throughout the body The patients generally get worse after sitting down or lying down awhile, and they get better on getting up and walking around

How Is the Pain Brought On?—Often it helps to know what factors tend to bring on a pain The pain of angina pectoris usually is brought on by walking, by exercise or by strong emotion The pain of cholecystitis may be brought on by eating too large a meal, by eating certain foods or by a tantrum of temper In some nervous persons violent abdominal pain can be produced by a tantrum Pain in the lower abdomen in nervous women usually is due to a mucous colic which, again, is due to emotion, unconscious tension, fear or worry Flare ups in ulcer pain are due often to strong emotion The pain of diaphragmatic hernia can be made worse by eating a large meal by bending over to tie the shoes or by lying down too soon after a meal The neglect of constipation can cause hunger pain in some persons Many abdominal distresses can precede or accompany an acute respiratory infection Some abdominal

needs in medicine today is for a wide dissemination of the knowledge of this fact that pain is a common symptom of psychoneurosis

As already pointed out one of the great characteristics of these aches is that they are not severe Often a woman will say that the ache is so slight that she would not fuss about it, if she knew exactly what the cause was and that she need never fear that it is going to 'turn into something' *A common characteristic of these aches is their constancy, day and night* Sometimes they are associated with local soreness Occasionally when a woman has a psychosomatic ache in the region of the liver she will remark on questioning that that whole side is bad so that she has some aching from the top of her head to the tips of her toes on the right

Some of the curious pains in the abdomen may be migraine equivalents The physician must suspect this particularly when the patient has a *migrainous family* a typical migrainous personality, a *history of* migraine in her younger years or a history that, as she grew *older* the headaches disappeared and the abdominal *component remained or got* worse

Epileptic equivalents are met with occasionally by gastroenterologists Sometimes one can suspect the presence of such an equivalent on noting the patient's red and rather sullen face and then getting from him a history of convulsive disorders in other relatives In such cases the electroencephalogram commonly shows a typical dysrhythmia

Abdominal Pain Due to Fear, Anxiety or Rebellion — It must be remembered that fear or acute anxiety or even chronic worry can produce abdominal pain many persons say 'fear tied me up in knots', or 'fear hit me in the pit of my stomach

Pains Due to Neurotropic Viruses — It is well known that one can suffer severe pain for days before an attack of the shingles and for months or years afterward and that such pain is due to injury of a posterior root ganglion by a neurotropic virus It is probable therefore that some of the curious neuralgia like pains felt in the thorax and abdomen are due to an infection with a neurotropic virus which fails to produce a herpetic lesion

Pains Due to Chemical Changes in the Tissues — It seems probable that many obscure pains for which no organic cause can be found are due to microscopical or chemical changes in the tissues For instance one of the worst pains that a man can suffer is that of gout in his big toe and as everyone knows this is due to the presence in the tissues of crystals of uric acid Many persons suffer with a sore liver and for years it seemed probable that this was due to some form of hepatitis Today with

probably react with distress or pain to its sudden distention by a toy balloon

The Diagnostic Value of a Sippy Treatment — It is unfortunate today that so few physicians know of the great diagnostic value of a few days of Sippy treatment If after forty-eight hours in bed on frequent feedings and all alkalization a patient with epigastric distress shows no sign of improvement, the physician immediately should suspect either that the person has not an ulcer, or that it is a complicated one which cannot be helped by any form of medical treatment

A Change in the Character of the Pain — When a man has suffered with hunger pain for many years a sudden change in the symptoms may mean much A severe pain coming suddenly may mean that the ulcer has penetrated into the head of the pancreas, and the physician can be more certain of this if afterward the patient no longer gets good relief from the taking of food and alkalies In other cases the complication that has come to change the syndrome is pyloric obstruction or a carcinoma

The Diagnostic Value of a Long Duration of Pain — Many a patient with pain in the abdomen and a tremendous fear of cancer can be reassured best by pointing out to him that he has had the pain unchanged for so many years that it can not have been due to a carcinoma If he had had one it would long since have caused obstruction or other symptoms leading either to the performance of an operation or to his death

Pain That Comes at Ever-Shortening Intervals — The patient with a psychosomatic type of pain often tells the story that he suddenly was seized by a pain years before The next attack came perhaps a year later and the next one several months later After that the interval became ever shorter until eventually the pain became a constant ache, day and night One practically never finds an organic cause for this type of abdominal pain Characteristic also of such pains is that they fail to respond well to opiates

Abdominal Pains or Aches Due to a Psychoneurosis or Psychosis — It is doubtless more than a coincidence that the constant and intractable aches in the abdomen for which no local cause can be found, usually are met with in unhappy tired sickly or more or less psychopathic women, many of them unmarried Physicians should always remember that one of the common initial symptoms of a psychoneurosis or psychosis is pain or aching Pain that is referred out to the periphery from the brain can be produced by a brain tumor psychic shock fear encephalitis thrombosis of an intracranial artery, migraine or epilepsy One of the great

duct to attacks of spasm in an irritable tract to food sensitiveness or to ordinary nervousness?

The most important thing to do in such cases is to find out if the patient had colics and a typical syndrome of cholecystitis before the operation Highly important is the question did the gallbladder contain stones and plenty of them If the patient did not have definite symptoms of cholecystitis, if the gallbladder was removed largely because of a roentgenological diagnosis and if no stones were found at operation the chances are that the original diagnosis was wrong and that the attacks now being complained of are not due to stones in the common duct

If the gallbladder did contain stones, did the surgeon explore the common duct and did he find stones in it? Did he drain the duct? If so it is very important to learn if drainage lasted longer than six weeks because this would suggest that a stone was left near the ampulla to produce some obstruction Naturally if many small gallstones were found in the gallbladder or in the common duct the chances are that *some were left* It may help to learn that the colics experienced since the operation are exactly like those felt before A history of an occasional chill fever and slight jaundice with the colics will add to the probability that there is a stone in the common duct Always in these cases it helps to estimate the amount of bilirubin in *the serum the day after a colic* it may then be found elevated perhaps also a little leukocytosis may appear

When pain returns after gastroenterostomy or gastric resection it is important to have the patient point to where the old pain was and where the new one now is felt Highly suggestive of a jejunal ulcer is a shift in the site of the pain from the right side of the epigastrium where it used to be to a point a little below and to the left of the navel This represents a shift from the duodenal to the jejunal area of reference on the abdominal wall When a pain returns to the old place in the epigastrium one should suspect merely a reactivation of the old ulcer

Pain Due to Fibrositis in Abdominal Wall or Arthritis About the Spine — One of the common causes of abdominal pain is fibrositis in the abdominal wall or arthritis around the spine involving the nerves that emerge from between the vertebrae Often if one asks the patient where he feels the pain he will admit that it is out in the abdominal wall and not deep in He knows that

In these cases it may help tremendously to ask and find that the pain has no relation to the taking of food In some cases it seems to be associated with flatulence but then it is hard to say whether the flatulence or the pain in the back comes first Sometimes pain in the right sacroiliac

the great experience that has come from studying epidemics of jaundice during World War II it is known that chronic hepatitis can remain for months after the acute stage of the disease has passed

Suggestive of a chemical cause for pain in the region of the liver is the fact that in one case in which a woman had a T tube in the common duct a severe attack of pain came at a time when the bile changed from the normal thin golden yellow fluid to a thick stringy blackish substance Evidently there had been some change in the metabolism of the cells of the liver

Typical gallstone colics can be observed at times in a person whose stoneless gallbladder has been removed and who is highly allergic to some food such as coffee or egg

Abdominal Pains Due to Vascular Disease — An example of terrible pain due to changes in the blood supply of a part is to be found in the case of frostbitten fingers that have to be thawed out Anyone who has gone through this experience knows that the pain can be agonizing

It seems probable that some of the vague undiagnosed pains met with in the abdomen are due to disease in arteries One knows how much pain can come from hemorrhage into a tissue from embolism in an artery or from thrombosis in a vein A woman who at intervals through the course of many years had suffered crises of terrible pain in the pelvis was found eventually to have a dermoid cyst full of the scars of old hemorrhages After the removal of the cyst she had no more pain Some localized pains in the abdomen may be due to patches of arteritis nodosa

Food Allergy — In some puzzling cases of severe abdominal pain, perhaps with violent nervous crises careful study will show that the storm is due to the eating of some food to which the person is highly sensitive As already noted sensitiveness to food can produce attacks of pain which are indistinguishable from those of gallstone colic

Adhesions — Many physicians and surgeons when puzzled over an abdominal pain make a diagnosis of adhesions but this appears to be unwise Certainly the results of operations for adhesions usually are disappointing In innumerable cases necropsy shows an abdomen full of adhesions which never produced either pain or indigestion Osler used to say "adhesions are the refuge of the diagnostically destitute"

Pain That Returns After an Operation — One of the difficult diagnostic problems often put up to a gastroenterologist is what is the cause of colics and pain which keep coming after the removal of a diseased gallbladder? Are these pains due to the presence of stones in the common

weeding a lawn In *some cases of pseudo-ulcer the symptoms are dependent upon psychic storms* Usually the pain disappears the day the patient goes on a vacation but this is not diagnostic because a patient with ulcer may have the same experience

Pseudo cholecystitis —There are many cases of soreness or pain or constant aching over the liver region in which the symptoms persist after the removal of the gallbladder and perhaps after repeated surgical drainages of the common duct Perhaps the colics and pains persisted when a T tube was in place *and this fact ruled out biliary dyskinesia as a cause of the trouble* In some of these cases in which colics came while a T tube was in place it could be seen that the pain was associated with a change in the color and viscosity of the bile It became blackish Often an ache in the region of the liver is due to fibrositis in the thoracic wall or to arthritic changes around the thoracic spine Occasionally one can find a case in which two of the lower ribs rub together and in which there is some arthritis in the little joints around the tip of the tenth rib *In some cases of severe colic the cause is sensitiveness to some food* In other cases the patient has a residuum of hepatitis following the epidemic form of the disease Occasionally with this disease there will be some fever

Pain Due to a Diaphragmatic Hernia —Diaphragmatic hernia of the congenital type is found fairly often when the roentgenologist is asked to look for it He commonly misses this lesion because he does not think *to ask the patient to lie down and strain One must think of a diaphragmatic hernia* whenever there is distress back of the heart associated perhaps with the eating of a large meal with lying down or with bending over to tie the shoes Sometimes the distress is relieved by sitting up Sometimes there is some dysphagia or severe heartburn Oftentimes the story suggests angina pectoris or gallstones, and in an occasional case one can find besides the diaphragmatic hernia coronary disease gallstones or heartburn Then *especially if the patient is a heavy eater* it is hard to know what is the origin of the distress and how much benefit would follow from an operation

Pain Associated with Cardiospasm —There is a puzzling type of severe pain which may come as a first sign of cardiospasm even before the dysphagia appears The distress may resemble that of coronary disease or of gallstone colic It may be so severe as to require morphine It may come with swallowing or at any time

Abdominal Pain Due to Colds and Infections —Many persons suffer with abdominal pain or soreness, an attack of acute indigestion severe

joint will be associated with an ache in the region of the appendix and some flatulence

As already pointed out, the characteristic feature of the pain of arthritic origin is its tendency to get worse when the patient rests and to get better when he gets up and walks. In some of these cases pain forces the patient to get up at daybreak and to walk around awhile

In many cases arthritic pain in the thoracic wall give rise to the false diagnosis of angina pectoris. The diagnosis of an arthritic or fibrositic type of pain is greatly strengthened when one gets the history of attacks of lumbago, cricks, wry neck, sciatica and generalized arthritis. It may help also to find roentgenological signs of arthritis about the vertebrae. Lack of such changes of course does not rule out the presence of mild arthritis. The severity of the symptoms complained of is not closely correlated with the severity of the changes in the bones

Occasionally one can detect the presence of fibrositis by lifting up a fold of the abdominal wall and pinching it. This may cause the pain that the patient is complaining of

Aches Suggesting Chronic Appendicitis —There are innumerable persons who often have an ache or soreness in the right lower quadrant of the abdomen for years after the appendix has been removed. Sometimes one can strongly suspect that the ache and soreness are part of the syndrome of an irritable bowel or so called mucous colitis. In such cases the cecum feels hard and is sensitive. In other cases the trouble seems to be due to fibrositis in the abdominal wall or to arthritis with injury to nerves. In some cases there may be myositis of the psoas muscle. In others the cause probably is up in the brain. Sometimes the pain is felt also in the left lower quadrant of the abdomen

Pseudo-ulcer —There are many cases in which the patient complains of hunger pain, sometimes so typical that it cannot be distinguished from that of ulcer. In other cases there are features which will make the experienced clinician suspect that there is no ulcer. In most such cases the roentgenologist's statement that there is no sign of ulcer in the stomach or duodenum must be accepted as correct. Some of these patients who have been watched for years have never shown any more signs of ulcer than they had to begin with and have never developed any complications of ulcer

In some cases the cause has been found to be sensitiveness to some food such as milk or eggs and in other cases the cause has been found to be chronic constipation with back pressure from the colon. In other cases the pain comes if the person eats too much or bends over as when

of this disease makes it much more probable that he has diverticulitis than that he has cancer of the colon The disease almost always involves the short segment of descending colon which runs into the sigmoid flexure In some cases in which this segment about 4 inches (10 cm) long, is almost made up of diverticula the pain appears to be due to spasm and not to infection, at any rate the leukocyte count and the blood sedimentation rate do not go up and no mass forms

Pain in the Suprapubic Region Due to Posterior Urethritis—Occasionally the gastroenterologist will be consulted by a man who complains of pain above the pubes This is likely to be due to chronic inflammation in the posterior urethra or perhaps in the prostate gland When this inflammation is cleared up the patient gets well

Prostatic Cramps—Occasionally a man will complain of severe cramp like pain which comes in the region of the perineum and lasts about five minutes During this time the victim may walk the floor in much distress It appears to be due to a cramp in the muscle of the prostate gland

Pain or Distress Which Arises in the Abdominal Aorta—There are some elderly women with a flabby abdominal wall who complain of a throbbing a beating a soreness or a pain which appears to be arising in a tender abdominal aorta

Pain and Soreness Arising in the Xiphoid Appendix of the Sternum—Some arthritic persons suffer at times from marked soreness around the tip of the sternum It appears to be due to a perichondritis.

The Side-Ache of Runners—Athletes sometimes suffer from soreness about the tip of the tenth rib which may make it almost impossible for them to do any long distance running The best explanation for this pain appears to be that given by Treves, who said it was due to arthritis of the little joints which connect the movable tip of the tenth rib with the end of this rib and with the ninth rib above That such inflammation can be present is shown by the fact that in some runners the skin over this region will become reddened and somewhat edematous and sore

Syndrome of Reverse Peristalsis

The physician should think of reverse peristalsis or a tendency to it in the stomach and bowel, whenever a patient complains of nausea with perhaps regurgitation water brash, heartburn belching a feeling as if waves were breaking back against the diaphragm, occasional hic-

mucous colic or so called intestinal influenza just before or after a cold appears At such a time any food eaten may cause gas and pain and distress

Mucous Colics—One of the commonest causes of abdominal pain, especially in nervous women is the mucous colic The patient usually has a sore tender colon and has exacerbations of pain with the frequent passage of gas and a little watery mucus from the rectum whenever she gets under psychic strain Even the slight excitement of going out to dinner, having a guest to dinner or going out with a beau can bring on an attack

The pain usually is felt below the navel Sometimes the discomfort can be relieved by the taking of an enema of 1 or 2 liters of warm water containing a tablespoonful of table salt Only rarely, when the colon is full of gas and is pressing up into the region of the stomach, will the distress be felt above the navel

Ulcerative Colitis or Stenosing Ileitis—Pain in the lower half of the abdomen with diarrhea and fever and perhaps the occasional passage of blood should make one think more of chronic ulcerative colitis or stenosing ileitis

Pain Due to Recurrent Attacks of Mild Intestinal Obstruction—Sometimes, and usually in persons who have had one or more operations, there will be attacks of intestinal obstruction in which there are rhythmic labor-like pains perhaps with the rising up of a loop of gut visible in the abdomen This loop will rise up and then go down suddenly with a gurgle In older persons such symptoms indicate obstruction of the gut due to carcinoma With the attacks there is likely to be constipation, perhaps some nausea and vomiting and perhaps much borborygmus The taking of food may cause pain promptly because of the surging of intestinal contents down against the obstructed place

Diverticulosis and Diverticulitis of the Colon—Diverticulosis of the colon is common and probably does not produce any symptoms, there is no reason to suspect that it should Diverticulitis of the colon is a rare disease which comes when a few of the colonic pouches become inflamed The usual symptoms are pain in the left lower quadrant of the abdomen with a sausage like mass there some constipation perhaps the passage of a little blood and usually a chill and some fever Sometimes because of involvement of the wall of the urinary bladder there will be frequency of urination If a fistula forms between the colon and the bladder, gas and a little feces will be passed through the urethra The fact that during the course of a few years a patient has had several spells

can be brought on in many ways, by excitement or emotion by getting angry by eating too much by eating certain foods by drinking certain liquors or by smoking too much Heartburn is discussed more in detail in a later section of this chapter

Waves Running Up the Esophagus—There are a number of distressing sensations which appear to be induced by waves or ripples running up the esophagus Such waves are likely to appear after the patient has eaten too large a meal The stomach then appears to send off ripples that go both upward and downward There are several types of belches with more or less distress Sometimes with the belching there may be a tendency to get hiccup or to gape Some of the waves gurgle as they reach the pharynx, or they will produce curious musical or squeaking or rubbing noises Some of these sounds seem to arise in the pharynx as an ascending wave reaches it

The victim may keep swallowing in an effort to force the waves back down again or he will chew gum to get relief or he will take a little solution of sodium bicarbonate or a little food Occasionally with a belch he will taste a little food which has come from the top of the stomach Sometimes an ascending wave will so strangle him that for a moment he cannot speak Often the symptoms can be brought on or exaggerated by bending over after a meal as when tying the shoes Occasionally a particularly loud and explosive burp will come up which will cause a digestive distress to cease for a time This will suggest that with the running out of a big wave an ectopic source of reverse waves in stomach or bowel quieted down

Nausea

Nausea probably begins most often in the duodenum or the upper part of the small bowel It is rarely complained of with disease in the stomach or esophagus It can be present in cases of cholecystitis and it can be the outstanding symptom in cases of slight obstruction in the lower part of the bowel When nausea comes in waves it may be that the patient is feeling actual waves of reverse peristalsis coming up the bowel That nausea is not produced by reverse waves traveling over the stomach or esophagus is indicated by the fact that it is never complained of by regurgitators ruminators and most belchers

Many frail overly senstive and tired women not pregnant complain of nausea in the morning or nausea which lasts for much of the day Occassionally a man will have the same trouble Such nausea appears

cups, actual vomiting, a feeling of fullness immediately after taking a few mouthfuls of food and a coated tongue and a bad taste in the mouth in the mornings In such cases a patient may complain that food lies too long in the stomach Physicians often look on this phenomenon as due to pylorospasm, but usually when the patient is examined with the roentgenoscope, no pylorospasm can be found The least push on the barium-filled stomach will cause it to empty into the duodenum Years ago, when surgeons performed gastroenterostomy with the idea of helping persons with such a slowly emptying stomach, they learned to their sorrow that they could not get it to empty any better after making a large opening into the jejunum Evidently something had gone wrong with the gradient of forces between the stomach and the bowel

Symptoms of reverse peristalsis may of course, originate in an irritating or obstructing lesion in the bowel, but they are seen more commonly in patients with nervous troubles and fatigue and a lifelong tendency to dyspepsia In such persons the waves seem able to run backward to the cardia and up to the esophagus about as easily as they run downward toward the rectum Something appears to have gone wrong with the underlying polarity or gradient of the digestive tract

The essential diagnostic point in many a case is that the patient has none of these symptoms of reverse peristalsis or of a reversed polarity of the gut and hence his distress or pain is not likely to be arising in the digestive tract

Regurgitation —It is tremendously important to question the patient, who says that she is vomiting to make sure that she is not just regurgitating, because this may make a tremendous difference in the diagnosis With regurgitation the patient brings up mouthfuls of food usually without any nausea or retching and often before she leaves the table In practically 100 per cent of the cases this is a functional disturbance In chronic alcoholics such regurgitation is spoken of as "water brash"

Heartburn or Acid Stomach —Heartburn is a burning or rending distress, which is felt along the course of the esophagus When asked to show where his distress is the patient with heartburn brings his hand to the epigastrium and then moves it up the sternum The distress appears usually to be due to the regurgitation of acid gastric juice into an esophagus which then becomes irritated and sore Attacks of heartburn come and go The disease is not necessarily associated with an increase in gastric acidity It not infrequently is found in persons with ulcer but in them it does not appear to be due to the ulcer

Heartburn appears to be an inherited and a functional disease It

Perhaps food is brought up that was eaten twelve or twenty four hours before In bad cases the patient cannot sleep because fluid is sloshing around in his stomach all night Perhaps then much weight is lost because the food cannot get out into the bowel to be absorbed

It is sometimes helpful to find out that the vomiting is never spontaneous but is produced by the patient sticking his finger down his throat *In such cases the trouble may be a nervous and functional one* Curious types of vomiting will be seen sometimes in migrainous persons

Vomiting can occur not only with disease in the digestive tract but *with disease in the heart kidneys gallbladder, spleen thyroid gland* ovaries uterus suparenal glands and perhaps any organ in the body

It is very helpful to find that the patient always vomits a watery, *often bile containing fluid and never any food This shows that there* is no obstruction at the pylorus, and that really the stomach is emptying faster than normal The vomiting of bile means only that there is reverse *peristalsis in the* upper part of the small bowel

Spells of so called bilious or cyclic vomiting, especially in children, are usually the equivalents of migraine The so called projectile vomiting of brain tumor is perhaps better described as being sudden or unexpected vomiting, not preceded by nausea It should make the physician think of increased intracranial pressure Vomiting with dizziness, coming in an acute attack, will suggest Meniere s syndrome with disease in the brain or the ear In older persons the sudden coming of nausea, vomiting and dizziness or vertigo, which is not associated with any sign of disease in the ear is likely to be due to thrombosis of some small intracranial artery

Globus

As is well known globus is always a sign of a nervous or hysterical temperament The fact that a woman has one definitely nervous symptom like this should make one suspect that some of her other symptoms are of similar origin

Salivation

Salivation may be associated with nausea Its causes are not well known *In some cases it is due to a sensitiveness to some food such as* chocolate Repeated swallowings of saliva can cause the bowel to be filled with air

to be nervous in origin and it may be that the sensation arises in the brain A patient can have such nausea for years without coming to any bad end

That nausea can be psychic in origin has been demonstrated in many ways as by women, who get this distress when they think they are pregnant and by men who are deeply sympathetic with a pregnant wife During the war soldiers became nauseated from fear and disgust and from viewing many dead bodies The thought is embalmed in the phrase, You make me sick

Nausea can be a marked symptom in some cases of food allergy It is experienced commonly by migrainous women In them the origin probably is in the brain Perhaps during sick headaches it is associated with reverse waves coming up the bowel from the region in the upper part of the jejunum which receives large branches from one of the vagus nerves Similar storms going down the vagus nerves may cause the nausea of patients with Meniere s disease and with thrombosis of small intracranial arteries Nausea has been produced by stimulation of the vagus nerves in persons studied under regional anesthesia

Nausea can come from the eating of much fat or from taking some mildly emetic drug such as digitalis or aminophylline In cases of chronic nausea the patient must be asked to give up the taking of all drugs for a time Nausea may be a symptom of using too much tobacco It can be produced reflexly by the distention of any hollow organ in the body It may accompany any severe pain, and it may be a sign of a failing heart It can follow any large hemorrhage which produces anemia It is severe in cases of mountain sickness It can be produced by the intravenous injection of certain amino acids

Nausea can be produced by unpleasant sights smells and thoughts and by disgust at the unattractive appearance of food Curiously when nausea is present, sometimes it can be helped or made much worse by lying on one side of the body or the other

In the case of a woman with nausea one must of course always rule out pregnancy Some women are nauseated at the beginning of the menstrual period

Vomiting

When a patient complains of vomiting one must always inquire to find out exactly what is meant Does the vomiting suggest obstruction of the pylorus? If so it probably comes hours after the food is eaten

A helpful point may be that after the passage of the tarry stool the patient's hunger pain and indigestion disappeared. This is a characteristic story in cases of bleeding ulcer. Especially if the patient was not weakened by the passage of a bloody stool one should inquire if he was taking some white powder, possibly bismuth, or if he was eating a large amount of spinach, beets or Concord grapes.

Red Blood in the Stools—Red blood in or on the stools always should make the physician think of carcinoma of the rectum or colon or of chronic ulcerative colitis. He should think of these diseases even when bleeding hemorrhoids are present. Blood on the toilet paper is more likely to be due to the hemorrhoids or to a fissure than to disease higher up in the colon. However, in every case of rectal bleeding an expert should examine with the sigmoidoscope, and if nothing is seen then a roentgenological study of the colon should be made. It is a sad fact today that a considerable percentage of the patients who come with an inoperable cancer of the rectum have recently been operated on for hemorrhoids or have been treated for amebiasis or dysentery.

Flatulence

As has already been pointed out, when a patient says that he is suffering from gas the physician must go into details to see what he really means. Does he belch, or does he bloat, or does he pass an excessive amount of gas from the rectum? *Serious belching usually is neurotic in origin and due to worry or fear.* All heavy belchers are swallowers of air, and many of them have no indigestion at all. They need to be treated by a psychiatrist and not by a gastroenterologist. No diet will help them. To be really flatulent the patient should have some indiges*tion or abdominal distress and an excessive amount of flatus.* The trouble may then be due to constipation, over eating, the eating of foods to which the person is sensitive, cholecystitis, a respiratory infection, stormy emotions or so called mucous colitis. Flatus that does not smell is likely to be swallowed air, while that which smells bad is more likely to be due to *indigestion*.

Flatulence is discussed in greater detail in a subsequent section in this chapter.

Borborygmus

Borborygmus or loud gurgling *in the bowel can be due to nervous*ness, to flatulence, to an irritable bowel, to emotion or to purgation. If

The coming of a sticky, ropy type of saliva should make the physician think of a brain tumor or a minor apoplexy

Rising Toward Daybreak to Move Bowels

There are a number of persons who have to get up about daybreak to pass gas or to have a bowel movement Sometimes the feces are soft The cause of this syndrome is not known It was once thought to be due to achlorhydria, but actually it seldom is, and the patient is seldom helped by the giving of hydrochloric acid The trouble may be due to hypersensitiveness of the patient or the bowel, to the eating of too much food at bedtime or to the eating of some food to which the person is allergic

Hematemesis

Hematemesis usually indicates the presence of peptic ulcer or gastric carcinoma but the source of bleeding may be the large esophageal veins resulting from cirrhosis of the liver, a patch of gastritis, purpura, a hemangioma or congenital telangiectases of the stomach, or there may be a bleeding diathesis Occasionally one cannot find any cause

Hemoptysis

Occasionally one will see a person who says that from time to time he brings up a teaspoonful of blood without either coughing or retching He does not know where it comes from Usually in such cases after the most careful examination of the lungs the esophagus, the pharynx, the stomach and the nose it is impossible to say whence the blood came

Melena

Tarry Stools —The history of a *tarry stool* usually is significant only if at the time the patient became weak Usually after a hemorrhage of any size the patient wants to stay in bed for from one to three weeks The hemoglobin should be found to be reduced In the worst cases the patient faints in the bathroom, or he finds himself unable to go up a flight of stairs

Dietary Indiscretions

Much indigestion is due to eating too fast, and much is due to eating too much Often the spouse has to tell the story because the patient will not volunteer the information that he makes a pig of himself at meals

Some persons are losing weight because they eat too little and many have been put on too narrow a diet or a diet without sufficient fat or protein

Drinking of Unnecessary Water

Today it is fashionable to drink much more water than the body needs, and this sometimes accounts for sleeplessness due to the patient's being waked several times at night to urinate Sometimes it accounts for an otherwise unexplainable diarrhea

Abuse of Purgatives and Other Drugs

Indigestion with flatulence abdominal discomfort and gurgling can be due to the taking of laxatives Some of the bulk producing drugs so popular today produce flatulence abdominal distress and bloating

Many nervous persons take bromides in too large doses Others are taking too much phenobarbital or dessicated thyroid substance In puzzling cases it is wise always to ask the patient if he or she is taking some drug and, if so what is it

Excessive Use of Tobacco or Alcohol

In some puzzling cases it is well to find out how much tobacco the patient is using Tabagism can cause poor health loss of weight quick pulse palpitation loss of appetite heartburn shortness of breath precordial distress nausea and hunger pain Often the experienced physician will guess from the patient's appearance that he or she is taking too much alcohol

Weak Spells and Fear of Fainting

Many women, who complain of weak spells or a tendency to dizziness or uncertainty are subject to migraine or are going through the

it appears for the first time in older persons, one must think of carcinoma of the colon

Loss of Appetite

Loss of appetite probably should be viewed always with some alarm especially in a person who previously has enjoyed his food In many cases, of course the trouble is transient, due to a cold, to some little infection or to some sorrow or anxiety In older persons one must think of the coming of some serious disease such as a cancer somewhere a small stroke heart disease a brain tumor tuberculosis, hypertension or nephritis A marked loss of appetite may be due to a beginning mental depression or an anorexia nervosa Occasionally loss of appetite may be due to the taking of some drug such as digitalis, to smoking too much, or to the extraction of many teeth Some persons cannot get used to dental plates easily

Whenever the physician has reason to fear the presence of cancer somewhere it is cheering to hear that the patient's appetite remains good This does not prove that cancer is absent but it suggests it It is a bad sign when a person, who has just parted with part of the stomach because of cancer fails to regain his appetite Metastasis then probably has taken place already

When a person complains of a vague indigestion, it may help to find out that he or she eats under unsatisfactory conditions Perhaps a man rushes out to a lunch counter wolfs down his food and runs back again to work Many men talk business while they eat Many a tired mother of several children has no interest in eating after she has been in a hot kitchen preparing the food

Loss of Weight

One must always look on a rapid loss of weight as a serious symptom unless it is found that the patient went on some inadequate diet or is losing edema fluid from the body tissues If there has been no change in the diet or no edema disappearance one must search for carcinoma hyperthyroidism diabetes nephritis, or pernicious anemia or in older persons one must think of a small unrecognized apoplexy Occasionally loss of weight is due to the taking of some drug Some of the most striking and rapid losses of weight are due to sorrow or worry

It is very helpful to find out if the diarrhea wakes the patient at night, because if it does, it is more likely to be due to some organic disease Great urgency with tenesmus indicates a lesion in the rectum

It is helpful to learn that a so-called diarrhea has been present for years without pulling the patient down because this suggests a functional trouble Often in such cases a soft diet has little influence on the number of stools in a day Oftentimes a patient with long lasting functional diarrhea is stout

Dysphagia

It is a curious fact that patients, who have difficulty in swallowing often forget to mention it. A long history of intermittent dysphagia suggests cardiospasm, while a short history of constant trouble suggests carcinoma

Distresses in the Mouth

Occasionally one sees an older woman, who complains bitterly of a sore mouth or tongue a burning in the mouth or an acid or a foul taste Sometimes the distress will be felt in only one half of the tongue or mouth In most of the cases no lesion can be found in the mouth and the impression left is that the trouble is due to some lesion in the brain or some nerve tract

Canker sores in the mouth often are due to the eating of some food to which the person is sensitive A common offender is chocolate

Food Sensitiveness and Allergy

In all puzzling cases of indigestion it is well to ask the patient if he or she knows of any definite idiosyncrasy to food Most persons have one or two foods which they know they must not touch and their symptoms may be due to the eating of some food which they have not yet suspected as possibly being an offender

Jaundice

When a person says that he has been jaundiced he should be cross-questioned to see if it was not just a sallowness that was experienced

menopause Some perhaps have a low blood pressure Others have an irritable carotid sinus Others are just nervous or constitutionally inadequate

Constipation

Constipation that has been present most of the patient's life naturally is not likely to be of much import Constipation, however that comes out of a clear sky in the case of an older person is a worrisome symptom, and it commonly points to the presence of a carcinoma at the pylorus or in the colon

It is always interesting to find out if the patient's indigestion is secondary to constipation Often after the taking of some castor oil or an enema, the patient will feel wonderfully well for a few days, and this fact will establish the diagnosis

Pencil or Ribbon Stools

It is hard to know if the passage of pencil or ribbon stools means anything Often all it means is that the fecal matter has become soft perhaps through the taking of hydrocarbon oil, and in other cases it means that the anal ring is contracted or too tight

Diarrhea

First one must find out what the patient means by diarrhea He may mean one soft or watery stool a day, many small hard stools the occasional passage of a little watery mucus with some gas or the passage of many bloody stools Naturally all these different complaints suggest different diseases

Suggestive of a functional type of diarrhea is the fact, often elicitable, that the patient and perhaps other members of his family have always had a tendency to get loose bowels when excited or worried Characteristic of a nervous type of diarrhea is the story that the patient usually has one or two loose stools and then is well again for a while In such cases the cause usually is a panicky fear Occasionally, however, such transient diarrhea is due to the eating of some food to which the patient is allergic

to be due to indurative or fibrositic changes in the muscles of the neck and scalp Many nuchal headaches are probably due to nervous tension The histaminic headache is generally a severe pain in one cheek associated with stuffiness of the nose on that side and perhaps watering of the eye The headache associated with a brain tumor is often of a deep aching dull and steady nature, it may be constant or it may let up occasionally It is seldom as severe as is that of migraine it rarely interferes with sleep Some headaches are due to injuries to the head Headache due to eyestrain is likely to come at the close of a day or after the eyes have been used excessively The let-down headache, which comes at the end of a period of strain may be of a migrainous type

More on headaches will be found in special chapters (Chapt XXXI A and XXXI B) on this subject in Volume VI

Focal Infection

Many worrisome patients go to the gastroenterologist complaining that they have a sinusitis, and that their postnasal drip is causing their indigestion They are convinced that the stuff that goes down the pharynx is toxic to the stomach Actually few of these persons have a true sinusitis but only an oversecretion of mucus in the nose Some are too fussy about it The material hawked out usually is not pus but a jelly-like substance The person who comes to the end of the day with a clean handkerchief, is not likely to have any sinusitis

Presence of Cardiac Neurosis

The fact that a patient has a typical cardiac neurosis suggests strongly that the abdominal discomfort or indigestion associated with it is also of nervous origin The same nerves that play tricks on the heart are playing tricks with the digestive tract

Diagnostic Significance of Irritable Bladder

Much can be learned about the bad state of a woman's nerves by learning that she must urinate every half hour during the day in spite of the fact that her urine is perfectly clear, and that she does not get up at night

Perhaps at the time, the urine was dark, and the stools were pale Perhaps there was an epidemic of jaundice in the town Young persons with jaundice usually have the epidemic form In older persons one will suspect the presence of stones or of a carcinoma in the head of the pancreas A history of colics in the gallbladder region then will be helpful Carcinoma of the head of the pancreas usually is accompanied by some pain but usually not a colicky one

Much itching, especially before the jaundice appears, suggests disease of the liver Jaundice, which steadily deepens and does not improve at all, suggests carcinoma of the pancreas or of the bile ducts

In the familial type of jaundice the pigmentation is not marked, and it is long lasting In many cases it is important to make sure that the patient has not been taking some drug such as cinchophen

It is usually easy to distinguish *carotinemia* because this does not make the conjunctivas yellow, it shows up most markedly in the calluses of the hands and around the mouth

Headache

Patients with headache commonly go to the gastroenterologist, hoping that he will find their trouble in the digestive tract Seeing that they seldom have any significant signs of organic disease in the head or in the body the differential diagnosis must be made by obtaining a good history The more common types of headache are those due to nervousness fatigue, traveling or being in a close room Some persons get a bad headache when hungry or when they have had to go without their morning coffee Other headaches are due to constipation These usually are relieved immediately by a bowel movement Some headaches can be due to taking too much alcohol the night before, others are due to eyestrain or disease of the eyes Commonly one observes a headache at the beginning of an infectious disease Many women get headache about the menstrual period Migrainous headaches are commonly on one side of the head and are associated with some nausea or vomiting and great prostration Such a headache usually is throbbing in character

The constant type of headache is a hard one to understand and usually no cause can be found for it Some headaches probably are due to a psychoneurosis The morning headache of hypertension is well known The headache of a sinusitis is more a pain in some part of the head Trigeminal neuralgia or tic douloureux is more a violent spasmodic pain in one side of the face than a true headache Many headaches appear

Dizziness Vertigo or Giddiness

Innumerable persons go to gastroenterologists complaining of dizziness or feelings of uncertainty lack of balance, fear of falling wooziness' or actual vertigo They think that the cause must be in the liver bowel gallbladder or stomach This probably is rarely the case If the dizziness or vertigo is associated with ear noises or some deafness it is likely to be due to trouble in the ear the eighth nerve or the part of the brain connected with the ear When the symptoms come suddenly out of a clear sky in a person past middle age and when there are no ear symptoms it is possible that there has been a thrombosis of a small blood vessel in the brain

Dizziness must be distinguished from feelings of uncertainty or mental haziness With vertigo things seem to spin around, or the patient feels as if he were spinning around Sometimes and especially when there are signs suggesting that the patient has had hypertension the physician should ask if anyone ever found the patient s blood pressure abnormally high Women who are subject to migraine, or who are going through the menopause sometimes will suffer from dizziness and a tendency to faint

Numbness

Numbness in an arm or leg often frightens a patient and makes him think he is going to get a stroke Rarely is this foreboding justified Older persons with hardened arteries often get numbness from lying on an arm or a leg Numbness in the legs or hands especially with tingling will make one think of a primary anemia A simple way of finding out if the arteries of the legs are patent is to ask the patient if he can walk some distance without pain If he can walk many blocks without distress he must have fairly patent arteries

Urticaria

The smaller lesions of urticaria can be due to the eating of some food to which the patient is sensitive Giant urticaria is more likely to be due to some heartbreaking psychic shock or worry or indecision

Hyperthyroidism and Hypothyroidism

Many of the patients seen by gastroenterologists have been told that they have hypothyroidism and have been given thyroid substance Often the basal metabolic rate has been reported as being −35 per cent

Insomnia

Many persons, who go to the gastroenterologist complaining of indigestion are really suffering most from insomnia Then the physician must find out what type of insomnia it is, and what are the causes that bring it

Nervous Breakdown

A high percentage of the patients who go to a gastroenterologist, are really suffering from a nervous breakdown Unfortunately they seldom think to complain of the typical symptoms In many cases, therefore, the physician must suspect what is wrong and must ask if the patient can work if he can read with comfort and ease, if he can sleep easily, if he can make decisions quickly and if he can control his emotions If he cannot do these things and if his disability is all out of proportion to the severity of his digestive symptoms and especially if there are changes in character, the main difficulty is a nervous breakdown, and the cause is in the brain

Then the physician must continue with the questioning to find out what brought on the nervous breakdown Was there much overwork or worry or strain or sorrow? Was there a death in the family, an automobile accident one or more operations or some debilitating illness? In older persons one must think of the possibility that the patient has had one or more small apoplexies In many cases, especially when the breakdown came without overwork or strain, it is important to find out if there was a bad nervous heredity This may have predisposed the patient to trouble

Fatigue and Easy Tiring

One of the commonest complaints of the persons, who go to the gastroenterologist for relief, is that of constant fatigue and feelings of weakness Seldom does one find a physical cause for these distresses Always one wants to know if the patient earned the fatigue by overwork or strain, or if it came upon him without such overwork It is very helpful to learn if the fatigue is felt in the morning before the patient gets up or if it comes toward the close of the day after much hard work In the first case it is likely to be due to a hereditary nervousness and in the latter case it may be due purely to overwork Most of the persons who complain most bitterly of fatigue have not earned it by working

jejunocolic fistula More rarely it is due to the performance by some would be surgeon of a gastro ileostomy

If a patient who has had gastroenterostomy performed for duodenal ulcer, is having hemorrhages it is essential to know if he had hemorrhages before the operation because if he did not, he is probably now bleeding from a new ulcer in the jejunum

Commonly, when a patient does not improve after some abdominal operation, it is because the diagnosis was mistaken, and the symptoms complained of were due to a neurosis constitutional frailness a nervous breakdown or sick headaches

The Family History

It is best to reverse the usual process and to take the family history last after the diagnosis is fairly certain The reason for this is that a good family history can be secured only after the physician knows exactly what he should look for If for instance, he suspects that an abdominal pain is an equivalent of epilepsy he will inquire tactfully and persistently about persons with fainting spells little forgetful spells or explosive tempers In this way he may hear of several cases of probable dysrhythmia If he had asked routinely if there was epilepsy in the family he would probably have been told no

Is Anything Left Unasked About?

Oftentimes after a history has been taken or an examination has been completed if the physician were to ask the patient what he or she really came for he would find that it was something entirely different from what had so far been discussed

After the physician is satisfied that he is dealing with an anxiety neurosis it is important to find out what the patient fears and why he so fears it Only when these questions are asked may the fact come out that some physician diagnosed coronary disease, or cancer of the stomach or possible syphilis Often the patient is pathologically fearful of a particular disease because he watched relatives die from it or he saw some one die from it after months of treatment for something else Because of this he is not assured when told that he has nothing serious

Unless the physician knows these things and knows how to deal with them his efforts at psychotherapy are not likely to be helpful Obvi-

Usually in such cases questioning will show that the patient usually a woman is mentally active and wide awake, often she is thin and nervous and unable to sleep well Under such circumstances it is most improbable that the basal metabolic rate was low and it could not possibly have been −35 *per cent* Much against the idea that she needed thyroid substance is the fact that when it was given her, it made her jittery and uncomfortable Usually *on getting* an accurate test or two, it will be found that the rate is around −15 *per cent* This is not due to hypothyroidism but to general frailness

Hyperthyroidism can often be diagnosed from the history of great nervousness, loss of weight, excessive perspiration, a feeling of abnormal bodily warmth a tendency to kick off the bedclothes, insomnia great feelings of fatigue *weakness in the knees* and perhaps, psychic disturbances and character changes

Sweating

Some persons complain of perspiring to excess but often they are stout and have neither signs nor symptoms of hyperthyroidism Their basal rate will be a little low and hence the sweating must be due to some nervous abnormality not well understood

Persons with cold clammy sweating palms are practically always tense and worrisome with overly active sympathetic nerves and a tendency to suffer from nervous troubles

The Patient Who Has Been Operated on

The patient who returns with trouble after operation often brings a difficult diagnostic problem and one that can be solved only by the taking of a very careful history Comment has already been made about the problems of persons who return with pain after cholecystectomy gastroenterostomy or a gastric resection

After gastroenterostomy or gastric resection some persons complain of symptoms that suggest a dumping stomach' Such a stomach is one which dumps its contents into the jejunum before they are changed in any way or even brought to body temperature Such dumping may produce feelings of fullness faintness giddiness or warmth perhaps with sweating and nausea or a desire to go to stool A mild diarrhea may be associated with the dumping stomach Rarely lientery is due to a gastro-

blood sugar or a spastic colon If the physician has satisfied himself already from the history and the appearance of the patient that he is dealing with a psychoneurosis, he is not so likely to be stampeded by the finding of a few amebae in the stool or if he knows the patient's troubles are all due to migraine he will not get excited about a slowly emptying gallbladder or even a normally functioning gallbladder which contains a cholesterin stone or two He will know that the removal of these stones will not cure the headaches, the hypersensitiveness or the constitutional frailness

Need for Diagnosing Exact Type of Functional Trouble Present

It is a highly creditable act when a physician diagnoses a functional type of distress and saves the patient from a useless laparotomy but he must not stop at that He must go on to find out what type of functional disease is present and what the disturbing mechanism is The routine giving of some phenobarbital may be good treatment in the case of a woman whose nervous indigestion is due to jitteriness and inability to rest but it will not cure the nervous indigestion of a woman whose nausea and heartburn are due to her smoking too much or to the eating of certain foods to which she reacts allergically Obviously each person must be studied enough so that specialized and appropriate treatment can be given

Types of Persons Who Have Functional Digestive Disorders

Now what are the common causes of functional indigestion and what are the common types of persons who get into trouble with their stomach and bowel?

The Highly Nervous—In a large percentage of cases of functional indigestion the patient is by nature nervous hypersensitive and over irritable Often he or she is a pathological worrier or fussbudget In many cases the indigestion has been brought on by the extra strain of overwork and long hours but oftener one must suspect that it is due primarily to a poor nervous inheritance Many of the most nervous or psychopathic or poorly adjusted of these patients are relatives of the insane This term classifies them well and probably explains the origin of their troubles

Persons With Nervous Breakdowns—Every gastroenterologist must watch daily for persons with a nervous breakdown It is unfor

ously he must find what the fear is, and then he must make a special effort to drive it out. He must make all those tests, which the patient feels are needed to rule out the presence of the disease he fears.

Functional Disorders and Digestive Neuroses

Definition

A large number of digestive disturbances must be called functional, because, if an operation or necropsy were to be performed, no lesion would be found in the abdomen to account for the discomfort felt there, or no gross lesion would be found in the digestive tract. There are innumerable persons in this world who suffer from indigestion all their days without any organic disease ever being found to account for it and without coming to any bad end because of it. Many have the abdomen explored several times, and many part with the appendix and the gallbladder and perhaps have a gastroenterostomy made, and still they suffer.

In a high percentage of the cases of indigestion, which he studies, the gastroenterologist must be prepared to make a diagnosis of a functional ailment and he must not put pressure on his roentgenologist to supply him constantly with placebos of diagnosis such as ptosis, spastic colitis, adhesions, a slowly empty gallbladder or a peculiar looking appendix. He must often be saying to the patient that his or her trouble is doubtless real, of that there can be no question, but it is not due to anything in the abdomen which at an operation the surgeon could find and cut out. This is the essential point.

An important point is that in such cases the diagnosis often must be made from the history and from the physician's size up of the patient. The diagnosis should be made positively, and because the physician recognizes a syndrome which he has seen many times before. There are symptoms such as burning in the epigastrium, "butterflies" in the stomach, quivering in the abdomen, the regurgitation of food immediately after eating, heartburn, distress immediately after drinking a glass of water, or sudden bloating immediately after drinking a bottle of pop, which are practically always functional in nature.

Too many physicians today try to make the diagnosis of a neurosis by exclusion. This is dangerous, because under pressure the laboratory technician and the roentgenologist are very likely to report some slight abnormality or some variant from normal such as a slightly lowered

blood sugar or a spastic colon If the physician has satisfied himself already from the history and the appearance of the patient that he is dealing with a psychoneurosis he is not so likely to be stampeded by the finding of a few amebae in the stool or if he knows the patient's troubles are all due to migraine he will not get excited about a slowly emptying gallbladder or even a normally functioning gallbladder which contains a cholesterin stone or two He will know that the removal of these stones will *not* cure the headaches the hypersensitiveness or the constitutional frailness

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tunate that today most of them go from one consultant to another telling their story in such a way that it does not occur to anyone that the essential feature of their disease is not the indigestion or the abdominal discomfort but rather some disturbance in the brain, which renders them unhappy, tired, weak and unable to work much if at all.

The gastroenterologist should often ask a patient, "are you working?" If the man says he can not work he should be asked why he can not. Usually then he will say that it is because he can not stand being around people, or if he tries to work a while, he soon gets nervous and jittery, perhaps the sweat breaks out on him, and he has to excuse himself and go off to lie down.

One of the best signs of a nervous breakdown is the fact that the patient can not read much. If asked why he can not read, he will say, that in the first place he has lost his interest in it, and in the second place his eyes tire quickly, the lines seem to run together, and he forgets the paragraph before he has finished reading it. Similarly he may not be able to sit through a movie. He will get tense and restless and will want to leave. A woman in church will always sit on the last pew so that she can slip out if she gets too tense and nervous.

These signs all show that something has injured the patient's brain far more than it could possibly be injured by any disease in the abdomen except perhaps carcinoma of the pancreas. Even a man with cancer of the stomach is likely to have an efficient active mind until he is pulled down by pain, undernutrition and loss of rest.

Once the physician is certain that the patient has, primarily, a nervous breakdown, the next question is how did he get it? Did he inherit it or did he earn it, perhaps by overwork or strain or worry? Helpful in deciding this question is: does the fatigue come in the morning or in the late afternoon? If the patient wakes with it and feels that he can hardly pull himself together to get out of bed, he probably has inherited a poor nervous system, whereas if the fatigue comes in the afternoon somewhat earlier than it should, it may well be due to overwork.

Usually when there is a nervous breakdown, the wise physician will pay little attention to the indigestion and will concentrate on efforts at helping the patient to get some rest or peace of mind. In difficult cases he will try to get the patient into the hands of a psychiatrist who can help him with his problems of adjusting to life.

The Psychoneurotic and the Mildly Insane.—Most gastroenterologists would be much surprised if they were to learn how many of the patients who are going through the office each month, barely missed insanity or

perhaps did not quite miss it These patients would not think of going to a psychiatrist but keep going to gastroenterologists because of pains aches and distresses in the abdomen

Some of them have a cyclic temperament which causes them to be too active and too talkative and energetic when they are in the up or manic phase and too depressed when they are in the down or depressed phase Other persons with a psychopathic tendency have poor self discipline so that for long periods they turn night into day and go without sufficient rest Then they collapse and have to hibernate for a while Many smoke too much they drink too much coffee and at night they may take too many sedatives in an effort to sleep

When slightly depressed they complain bitterly of the morning fatigue loss of pep feelings of intoxication and aches all over It is only on talking to them for a while and asking them about their up and down swings that one gets the typical history and can see the clinical picture in its entirety

The gastroenterologist sees also a number of rather sullen shy, reserved or inarticulate persons who barely missed schizophrenia They seem unfriendly and are hard to get acquainted with Often they are troubled with symptoms which are due to nervous storms in the autonomic nervous system their nerves are playing tricks on them

Then there are the hypochondriacs who never can be entirely reassured or cheered up They are convinced that they have a cancer or heart disease or that their brain is being poisoned by toxins coming out of the colon These persons generally are incurable No amount of reassurance convinces them Somewhat psychopathic also are the women who get terribly tense unreasonable and impossible to live with for a week or so about the time of menstruation and the women who go to pieces nervously and become somewhat depressed after the menopause The essential point to remember about many of these persons is that their trouble is nearer a psychosis than an ordinary neurosis or fatigue state or chronic nervous exhaustion

In many cases it would seem that the patient s storms in the autonomic nervous system correspond to the insanity in a near relative It is known today that disease of some parts of the brain and particularly of the hypothalamus and the third and fourth ventricles can cause loss of appetite vomiting and abdominal pain and can lead to the production of peptic ulcers One must remember that abdominal storms are associated with seasickness migraine Meniere s disease brain tumors, epilepsy the minor apoplexies and locomotor ataxia

To aid his mental development the internist should look occasionally into a book on mental diseases or a journal of psychiatry and glance over a few case histories to see how often when insanity begins insidiously, the earliest symptoms are so suggestive of some abdominal disease that the patient is operated on

The Constitutionally Inadequate —One of the commonest diseases seen by the gastroenterologist is constitutional inadequacy or frailness which throughout a lifetime makes it hard for the patient to stand up to the stresses and strains of life Many of these persons are relatives of the insane and their primary trouble seems to be that they have a poor type of nervous system Most of them complain of indigestion of some kind or of distresses in the abdomen and in other parts of the body Their problems will be discussed in more detail farther on

The Dyspeptic —There are a large number of persons who appear to have been born to be dyspeptics all their days, just why, it is hard to say Typical is the case of a small, thin man, a physician, who throughout a long life could never eat very much at a time and could not digest that unless it was cooked very simply His trouble could not be ascribed to nerves because he was an unemotional happy person, a tireless worker, who did not seem to have a nerve in his body When he died at eighty four a necropsy showed nothing that could explain the lifetime suffering from indigestion

Of course many of these dyspeptics are nervous, worrisome, hypersensitive persons, and some of them perhaps are allergic to a number of foods Many are constitutionally inadequate, but some are stout healthy-looking persons who are always belching and suffering with heartburn Some are thin, sour-looking finicky persons, who are always fussing about their food and certain that it will give them indigestion Some give up one article of diet after another until they get to living on little besides milk and toast Many will say they cannot touch anything raw, anything acid, anything fried anything that contains roughage or anything warmed over or canned Often their food will fail to digest properly if the conditions under which it is eaten have been unpleasant

Some dyspeptics fall in the group of health food faddists and some of these are on the lunatic fringe of society In others there may be some inborn defect in the mechanisms of digestion which causes them to function poorly throughout life In some the polarization of the gut or the gradient, which causes the waves to run easily toward the rectum, is developed so poorly that it is easy for waves to run upward toward the mouth That the basic defect is sometimes a hereditary one is shown by

the fact that in some families a number of persons are affected in the same way

The Small Laboratory People—There is a type of dyspeptic who may be called the small laboratory person because his indigestion comes whenever he eats much of anything It would seem that his powers of digestion are limited and that his stomach and bowel are like a small, poorly manned chemical laboratory which can handle only a small amount of work at a time It may be that some of these persons have a short bowel more like that of a carnivorous animal than that of an herbivorous one Others have a flabby intestinal musculature or perhaps, a poorly developed or atrophic gastrointestinal mucosa Some of these persons have no gastric juice and it may be that with this they have too little intestinal juice Perhaps the pancreas or the liver does not work efficiently

Some day studies should be made to see if in these persons an actual defect in the absorption of food gas or fluids can be demonstrated Some of them may have a defect in the mechanism which normally takes gas out of the bowel and excretes it through the lungs Some of these people have a stomach that empties rather slowly and this gives them distress if they eat very much

Factors in Causation of Functional Disorders of Digestion

Indigestion Due Possibly to Injuries Left in the Abdomen by Severe Disease Suffered Early in Life—It seems probable that in some cases perhaps in childhood the nerves of the digestive tract were injured by some neurotoxin such as is produced by the viruses of poliomyelitis encephalitis or herpes or the bacilli that cause diphtheria It is known that at times poliomyelitis will be followed by severe constipation According to Etzel and others in Brazil Auerbach s plexus degenerates in some persons if the proper amount of vitamin B in the diet is not available

Certain it is that in some persons the waves do not go easily and normally down the bowel but show a tendency to come back up again Evidence obtained in Ivy s laboratory indicates also that in some persons there is a tendency for contractions to appear in the bowel contractions which do not always move peristaltically but stay in one place for a time and there cause pain and a feeling of gas pressure

It is possible also that some injury to the gut can be left by a severe attack of bacillary dysentery One often sees patients with long lasting

indigestion or diarrhea which can be traced back to an acute attack of what was thought to be food poisoning or dysentery

A Defective Liver—When one remembers how numerous and important and complicated the functions of the liver are, one must wonder at times if the layman is right when he maintains that his indigestion is due to a sluggish lazy or badly functioning liver Theoretically there should be many diseases of the liver besides those few which we physicians can now recognize

For years a good argument against the idea of a lazy liver has been based on the fact that many persons suffering from an extensive but well compensated cirrhosis of the liver do not complain of indigestion But now the experience gained during World War II has shown that following an attack of epidemic jaundice the patient can go on for months with a chronic hepatitis which causes soreness of the liver and indigestion It may well be also that many of those persons who continue to have distress and flatulent indigestion and a sore liver and even colics after cholecystectomy owe some at least of their distress to the hepatitis with pancreatitis which was observed at the time of operation

A Defective Pancreas—It is conceivable that some forms of indigestion and epigastric distress are due to a defect in pancreatic function Rather against this view is the fact that some persons who are dying with carcinomatous destruction of the pancreas complain only of pain and mental distress

Disease of the Portal Vein—When one remembers that the portal vein is the life line of the body through which a man gets practically all of his nourishment it would seem as if there ought to be some diseases due either to a poor circulation through this vein or to some disturbance in its function Against this view is the fact that many persons with marked cirrhosis of the liver and much stasis in the portal vein have a good digestion Some may have a little flatulence Even when the portal vein gets partially thrombosed, it is surprising how well some of the patients get by for a time

Disease in the Arteries of the Bowel—One can often find in roentgenograms the shadow of a calcified abdominal aorta but this seems seldom to be associated with any discomfort in the abdomen Occasionally women past middle age will complain of a soreness in the abdomen which appears to be arising in a tender abdominal aorta It may well be that an arteritis nodosa occurs at times in the abdomen where it can produce pain and puzzling symptoms

Disturbances in the Flow of the Intestinal Lymph—The flow of

intestinal lymph through the lacteals of the mesentery and on through the thoracic duct into the blood stream must have some importance but as yet almost nothing is known about it either in health or disease

Indigestion due to Reflexes from Disease in the Lungs, Heart, Urinary or Generative Organs—It is well known that indigestion is likely to be associated with disease in other organs Disease in the heart with failure in compensation is very likely to produce nausea and flatulence and sometimes vomiting A stone going down the ureter can fill the intestine with gas and can produce nausea and vomiting

Many an appendix has come out unnecessarily because there was infection in the right kidney or a stone going down the right ureter In rare cases nausea and vomiting can be due to prostatic hypertrophy which has dammed back the urine and has led to an increase in the blood urea Disease in the prostate gland and the posterior urethra sometimes causes pain above the pubes and other distresses which will confuse the gastroenterologist Tuberculosis in some part of the urinary tract sometimes will send the patient to the gastroenterologist who for a time may be much puzzled

As everyone knows painful menstruation can produce nausea vomiting and diarrhea Endometriosis can produce transient constipation Because of the close relation between the pelvic and the digestive organs the gastroenterologist must often call on the gynecologist for help

A diaphragmatic pleurisy or a patch of pneumonia in the right lower lobe can easily simulate acute cholecystitis Even tuberculosis of the right upper lobe of the lung can at times produce a clinical picture suggesting that of cholecystitis

Endocrine Disturbances—The functions of the digestive tract can be upset by disease in the glands of internal secretion particularly in the thyroid gland the ovary and the suprarenal cortex One of the most striking symptoms of a crisis in Addison s disease is violent vomiting

The Irritable Bowel Syndrome Commonly Called Mucous or Spastic Colitis—Because this condition is described in Chapter IV only brief mention will be made here of the fact that one of the commonest of the functional troubles of the digestive tract is that in which the colon is contracted and sore to the touch and the patient is complaining of distress in the lower half of the abdomen In this disease there is no true colitis and the bowel never shows any sign of inflamation The condition tends to recur throughout life and usually is associated with the passage of mucus and a little water and gas The patient usually is

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Disturbances in the Flow of the Intestinal Lymph—The flow of

Pseudocholecystitis —There are a number of patients with a normally functioning gallbladder and symptoms which strongly suggest the presence of cholecystitis or even gallstones In a small percentage of cases of course operation will reveal stones in the gallbladder or the common duct but in most cases an operation will reveal no sign of disease and if the gallbladder is removed, the patient will go on with the old distress Usually the patient has a sore or tender liver and sometimes some indigestion It is possible that some of these persons suffer with hepatitis In others and especially in those in which the trouble is a mild ache which has been constant over many years, the distress probably is a psychosomatic one arising in the brain In some cases the trouble is in the external abdominal wall and is due to a fibrositis or to arthritis around the spine In a few cases the trouble is due to food allergy A test for liver function can be helpful in the diagnosis

The Postcholecystectomy Syndrome —One of the difficult diagnostic problems that the gastroenterologist faces from time to time is that of the patient, who after cholecystectomy continues to suffer or after a period of relief suffers again from indigestion flatulence soreness or aching in the right upper quadrant of the abdomen and perhaps even from colics Hints for the care of these patients are to be found in the section on pain in this chapter and again in Chapter IV Especially when the gallbladder was removed without good cause the trouble is likely to be a psychosomatic one

Adhesions —Many a physician or surgeon puzzled over the nature of an abdominal distress takes refuge in the diagnosis of adhesions and proposes an operation This is usually unwise because adhesions are common and rarely cause pain They are formed after most abdominal operations and many of them soon pull out or loosen up They rarely interfere with the passage of food through the bowel The wise physician will not make the diagnosis of adhesions unless perhaps there are signs of intermittent intestinal obstruction

Indigestion Due to Eating Under Bad Circumstances —Some irritable and overly sensitive persons who complain of puzzling attacks of abdominal pain get into trouble because they eat when they are upset nervously or are tense or fatigued A highly sensitive and musically inclined woman one day in a restaurant saw a young man come in with a large and ugly birthmark covering half of his face Her husband who was with her noted that she reeled somewhat under the impact of this sight She was much upset by a combination of disgust and sympathy

constipated and often the feces are ovulated The patient is tense, sensitive and nervous He or she may be calm externally, but there is a tendency to seethe internally and to tighten up in the presence of any strong emotion Mucous colics with pain tend to come under the influence of emotion or worry Oftentimes they come when the patient has a cold or other slight infection and then again it may be impossible to say why a particular attack came when it did

It will be a great day for medicine when roentgenologists stop reporting a spastic colon and physicians stop using the term "colitis" for two diseases one a harmless neurosis and the other a serious and often fatal inflammatory disease We should remember that every self-respecting, nervous and constipated woman has a spastic colon To remark on it and give it an alarming name can only add to her anxieties

Distress or Pain in the Right Lower Quadrant of the Abdomen —As is pointed out in Chapter IV under the heading of pseudoappendicitis, there are many persons who complain of pain and soreness in the region of the cecum Sometimes this part of the colon feels hard and tender In these cases unless the patient has had recently one or more attacks of fairly definite acute appendicitis it rarely does any good to remove the appendix Unfortunately in most cases by the time the consultant gets to see the patient there has already been a futile appendectomy

In some cases the soreness of the cecum appears to be part of the soreness of the whole colon In others the soreness is in the abdominal wall and is due to fibrositis myositis or arthritis about the spine In yet other cases there may be a myositis in the psoas muscle a sacroiliac arthritis, or the distress may be a psychosomatic one referred out from the brain Always in these cases disease in the right kidney and ureter should be ruled out by a urologist

Often the fact that the distress is not related to the taking of food, to the emptying of the bowel with laxatives or enemas or to the passing of flatus will show that it has no relation to any disease of the digestive tract

Pseudo ulcer —The physician must remember that many patients have a syndrome that closely resembles that of ulcer with attacks of hunger pain occurring from time to time In these cases the roentgenologist cannot see any ulcer, and none can be found at either operation or necropsy With the passage of time these persons do not develop an ulcer The condition is discussed at length in Chapter IV The common causes for the distress appear to be nervous influences constipation with back pressure toward the stomach and sensitiveness to some food

Rumination —Rumination generally is classed under the head of neurosis but in most cases it seems hardly to be a disease It may be only an inherited peculiarity A woman will regurgitate and because the food does not taste bad she will chew it and swallow it again So long as it does not annoy or prejudice the relatives, it should not cause any concern

Treatment of Functional Disorders of Digestion

Psychotherapy

One of the greatest needs in medicine today is for a constant awareness on the part of physicians of the fact that at least a third of the persons whom they see each day with digestive troubles are in need of some psychotherapeutic help Some physicians are so organically minded and were so trained in college that they will hardly admit that there is such a thing as a functional disturbance As one young assistant professor of medicine wrote to admit this is to admit diagnostic ineptitude and a lack of sufficient thoroughness in examining patients A professor of surgery used to begin his course of lectures with the statement that 'there is no such thing as a functional disease Partly as the result of this sort of teaching one can see every so often a psychopathic, constitutionally inadequate woman with her abdomen marked by the scars of six or seven futile operations all testifying to the fact that there are surgeons about who do not recognize the typical syndromes of psychoneurosis or mild insanity when they see them The experience of physicians with soldiers during World War II did much to wake some of them up to the fact that psychic disturbances resulting in symptoms of indigestion are common

After a physician has come to realize that a large percentage of his patients have psychological problems and after he has learned to recognize a number of functional syndromes, the next thing is to learn something about handling these patients and helping them back to health It would be well if many of them could be turned over to the type of psychiatrist who is interested in the sane but unfortunately there are not enough of such men to go around The problem is enormous, and every man in every specialty must learn to handle the types of neurosis which he sees every day

The Problem of Convincing the Patient that the Troubles are Functional —As every young physician soon discovers when he starts to practice medicine it is often very difficult to convince a psychopathic

Soon she began to have indigestion and about midnight she vomited the meal

Often a man who has traveled some distance to a medical center where he has had to wait around for a week or two, will report to the physician that on leaving home all his old pain, indigestion and perhaps, diarrhea cleared up Perhaps in order to bring on an attack to show the physician the patient has eaten all sorts of indigestible food but without being able to bring on the usual distress Obviously the reason for this is that the patient has been at rest and has been away from the disturbing influences in business and home that were causing all his trouble, he has been eating without tension and annoyance

Indigestion Due to Poorly Prepared Food —It is probable that many persons are correct when they say that their indigestion is due usually to the eating of greasy or poorly prepared food Many sensitive persons are upset also in a poor restaurant where the food is served unattractively If they think that the food eaten was of inferior quality, spoiled or contaminated in any way they will want to vomit it Some persons of a neurotic and worrisome type will admit that usually when they eat they expect the food to poison them

Indigestion Due to Eating Too Much or Too Fast —Often when the person who is complaining of indigestion is stout, the spouse, if asked will testify that the trouble is due to an abnormal appetite and a tendency to eat a great deal too much Sometimes the patient also eats too fast The result is repeated belching heartburn or regurgitation perhaps with bloating and the passage of much foul flatus Apparently the powers of even a strong stomach and bowel can be overtaxed and overwhelmed

The eating of large amounts of fat can produce nausea

Tabagism —It is probable that the diagnosis of tabagism is often missed by physicians Tabagism should be thought of whenever a man or a woman is complaining of chronic cough ill health perhaps loss of weight, a rapid pulse shortness of breath, nausea heartburn indigestion or abdominal distress Sometimes then if questioned the spouse will say that the spells of distress tend to come when there has been an increase in the amount of smoking chewing or taking of snuff A large number of persons in the United States use great quantities of snuff and they practically never mention this when their history is being taken

Biliousness —Many persons complain of biliousness, and it is hard to say just what they mean by it Often it is only a layman's term for chronic indigestion, constipation or migraine In rare cases there may be some hepatitis

ment and joy when her aviator son flew in unannounced from Europe or Japan

What Is Meant by Nervousness?—Often the physician's success or failure in his attempts to help a woman will depend on his ability to make her understand quickly what he means by nervousness and especially that he does not mean that he considers her stupid, flighty, excitable hysterical or foolish or thinks she is malingering He must insist that he is sure that her troubles are not imaginary, he knows that she is suffering and he sympathizes with her Perhaps he can say that he has noted that outwardly she is calm but perhaps her tense neck muscles her sweating palms or her tremor show that she is inwardly tense seething and near to crying Often the physician must explain that the calmest type of person may be one in whom any emotion is likely to disturb the functions of the inner organs Recently the writer saw a professional football player who with all his powerful frame and huge muscles had the overly reactive autonomic nervous system of his highly neurotic mother and was suffering with an irritable mucus forming bowel

Often it is helpful to make a woman realize that many of her troubles are due to her poor nervous heredity Perhaps she has long feared that she would go insane as some of her relatives did and it may encourage her to make her see that she has already gotten her share of the family curse

Often it helps to point out to a nervous person that he would never have achieved his success in life nor have had the pleasure he has had in his great appreciation of beauty in art and music and literature if he had not been somewhat neurotic He would have been much more comfortable if insensitive and stupid but then he would have missed much in life

Hypersensitiveness—Often the physician must point out to an overly reactive woman that she must suffer to some extent just because she is so sensitive Sounds smells bright lights the murmur of crowds jazz, raucous voices even the ticking of a clock may be distressing to her The many impressions beating in on her too sensitive brain wear her out

Also because of this great sensitiveness the patient often becomes unpleasantly conscious of the workings of organs which she ordinarily would not know she had When so tired that her threshold for sensation has dropped she may feel her heart beating or she may hear the whirring of blood in the carotid artery as it passes by the inner ear or she may feel the writhing movements of her intestine or the contractions of the little muscles that move the hairs of the skin The mere effort of putting

woman that she has not anything physically wrong to account for all her aches pains and feelings of fatigue She may refuse to accept the diag nosis of a functional disturbance and it may be a big problem to get her out of the office in a peaceful mood She and her family may decide that the most logical thing to do is to start right out looking for another physician who will make many more tests and who will find the one localized cause which they feel must be there to account for all her troubles

If only because of this great difficulty in convincing persons of the functional nature of their troubles, and because of the danger of antagonizing them and causing them to look on him as an ignoramus and an incompetent, and because it takes so much time to help these people, the physician is tempted to get rid of them quickly by giving them some placebo of diagnosis such as ptosis spastic colon or brucellosis Then he gives them as a placebo of treatment a prescription for some vitamin or whatever medicine happens to be the fad at the time and ushers them to the door The trouble with this of course, is that it doesn't cure the patient, soon he or she will be moving on to another physician who will repeat the process with a slightly different set of placebos

The Physician Must Convince the Patient That He Realizes She Is Ill, He Accepts This Fact and Is Sympathetic —There is something wrong with every person who is ill, but often it is not anything which could be demonstrated, if a surgeon were to cut into and carefully explore the part that is aching This is the essential point Patients can be reminded that many a complaining woman has her abdomen explored half a dozen times without any cause being found for her distress It may help also to remind persons with an ache in the abdomen that many people suffer all their days with an ache in the head and never come to any bad end They know that there is no use cutting into the head because as they say, 'it's just a headache or a neuralgia' Others can remember that after a stroke an arm or a leg will not function well, and yet it looks all right and there is nothing wrong with it Some patients have to be reminded that when they get frightened they may have diarrhea, or as they say their stomach is tied up in a knot Disgust can produce nausea, and a mental shock can put a stop to menstruation and can bring a menopause in the early thirties Many women faint easily with any strong mental impression and everyone knows how the heart can palpitate under excitement Sensitive women can vomit from disgust or even from excitement Many a woman vomited from excite-

has to continue unabated over months or years How easy then for the woman to develop a contracted bladder a chronic diarrhea, an irritable heart or a chronic indigestion

In some cases severe emotion appears to produce organic changes in some organ of the body, and as a result the patient will show up with a crippling arthritis exophthalmic goiter diabetes, a severe neurodermite or a peptic ulcer In some cases death itself may result

The Patient With Functional Troubles Suffers Greatly —As already stated, in starting any treatment of a patient with a functional distress it is well that the physician assure him or her that there is no question about the fact that the suffering is real Actually it is a sort of paradox that the very severity or constancy of a distress will make a wise physician almost certain that the disease is a functional one Why? Because the symptoms of so many organic diseases tend to come and go Usually a person with a painful duodenal ulcer complains much less than does one with a functional disturbance such as that due to a hypersensitive colon The man with the ulcer may have to be dragged to a physician by his wife, he may admit that some nights he does walk the floor with pain but as he says I can take it' The other patient with an occasional mucous colic may keep running to physicians and talking at length about his many troubles which seem to him to be almost more than he can bear

Nerves Playing Tricks —In the case of those many persons who are suffering from sudden panicky or jittery spells it may be helpful to point out that, when persons are nervous or tired little regulatory centers at the base of the brain seem to get out of control and then they send out storms along the nerves which upset the functions of perfectly normal organs such as the heart, the stomach or the urinary bladder One can point out to the victims of these storms that their unruly nerves are playing alarming tricks on them but because their essential organs are sound they will not come to any bad end

Sometimes this conception of unruly nerve centers is a great comfort to a woman in that it takes away from her some of her sense of guilt in regard to her nervous symptoms with the new explanation she does not have to be so apologetic or defensive about them She can have less fear about them and more hope of getting rid of them some day when she gets rested

The Explaining of Great Fatigue —One of the most difficult problems in handling many patients is that of explaining why when no organic disease has been found they are so painfully tired This question is particularly hard to answer when as the patient points out he or she has

up with such sensations and not getting alarmed over them may add greatly to the sum of the day's fatigue

Much of such hypersensitiveness usually is inherited but in many cases it is made worse by fatigue and illness As many a layman says, when he gets tired his nerves get on edge and then the stream of sensations which comes in constantly from the outside world, becomes a terrible burden Many persons then crave solitude and an escape from the world It may be distressing just to have another person in the room As internees in war prison camps have said, their greatest torture came from the lack of privacy

Exaggerated Reflexes —Sometimes it is helpful after eliciting greatly exaggerated knee jerks to point out to a nervous woman that with such heightened reflexes she must suffer simply because she reacts too violently to all stimuli

Too Great an Emotionalism —It must be pointed out to many nervous persons that they suffer also because their strong emotions are constantly racking them They are too sympathetic or too partisan, or they get too violently outraged at many things Many, and especially many who belong to certain racial strains are inclined to fly into rages and thus often makes them ill Many of them are too greatly distressed and upset by misfortunes which have come to other members of the family

Some persons have so vivid an imagination that they can relive old and painful experiences and can anticipate and see themselves and their loved ones going through all sorts of illnesses and disasters If they feel a little pain anywhere they promptly see themselves dying from cancer or heart disease Instead of fighting such a tendency some persons seem to cultivate it

Too Great a Suggestibility —Many persons are so suggestible that they are like the student in medical college who promptly gets the symptoms of every new disease that he meets

If Acute Fear can Cause Symptoms, Chronic Fear Can Also Do so —When the physician is trying to get a woman to see that her troubles might well be due to painful emotion it may be helpful to remind her that since acute fear can easily produce distressing symptoms chronic fear which is worry might also cause trouble For instance a woman who is acutely worried over the illness of a child may urinate every twenty minutes she may have diarrhea her mouth may be dry her heart may palpitate there may be a lump in her throat she may lose appetite and be unable to digest her food Let us say that the child's illness proves to be tuberculosis of the lungs and because of this the mother's anxiety

of the body Some have headache others indigestion, insomnia, backache anginoid pain or palpitation Such a person must remember that, when kept under great strain for years, the body has to break somewhere and different bodies break in different places

Why Did the Nerves Break Down When They Did?—Often when a woman is told that she is primarily a constitutionally inadequate person who was bound to break down some day she will refuse to accept this idea and will point out that she was strong and well until around the age of twenty two or twenty five when perhaps she started to teach school or had an unhappy love affair her first child an operation or a divorce Since that time she has had one illness after another There are several explanations for this delayed breakdown One is that it is characteristic of many constitutionally inadequate persons to get along well or fairly well until the first big strain comes Sometimes they break down about the end of the college course even without obvious strain They behave like a defective tire that has at least . 000 or 3 000 miles of service in it

Some persons break down apparently from the working out of a psychopathic inheritance which catches up with them as it did with some of their ancestors Another answer to these persons who break down without apparent cause is that perhaps they have not been entirely honest with the physician in that they have not told him of all their sins sorrows and painful mental processes They will not have mentioned an unfortunate love affair ending in a broken engagement or an abortion or a tragic marriage and later divorce Or they have said nothing of a very unhappy youth, of great feelings of inferiority or of a temptation to suicide

Oftentimes young people break down about the time they finish college largely because they overdid so terribly Perhaps they worked their way through or they were too active in extracurricular activities or they tried too hard to get high honors, they burned themselves out within a few years Then perhaps they tried to rest bu they could not turn off the stream of consciousness or they had to worry about finances or they could not find a comfortable haven in which to rest, so they did not get any better

What the Physician Might Learn if Only He Could Live for a Day in the Patient's Home—Often if a physician could only go into the patient s home for an hour or two or for a day he would see very clearly many of the factors which have brought a nervous breakdown and are keeping it going He would see difficulties perhaps with a problem child or with a mother in law in the home or with a difficult husband or he

not been overworking and at first glance has not had any unusual mental strain

It may help a bit to point out to such a patient, when he or she comes in, that one of the commonest problems put up to the consultant every day is just this one of severe distressing fatigue, for which no cause can be found Perhaps the physician should say that, if the patient desires a most thorough examination, and this is generally what he desires most, he can have it but he must brace himself for the probability that it will not reveal anything significant The physician does not expect it to reveal anything, because already from the history he has recognized a neurosis perhaps inherited from some psychopathic or occasionally depressed ancestor In other cases the history will have brought out the fact that for years the patient has overworked or has lived under distressing conditions well calculated to produce a neurosis

Often when a woman keeps insisting that all her troubles must be due to some abnormality that roentgenologists have reported in the gallbladder, appendix or colon, the physician must point out that there is no known disease of the digestive tract which a stoutish, healthy-looking person like her could have had for years that could have produced all her feelings of exhaustion and nervous breakdown Even if she had gall stones as big as hens eggs, they might produce pain and indigestion but not a nervous breakdown The physician can point out also that many a person with an abdominal disease as bad as carcinoma of the stomach or colon will continue for months to look well and to feel well enough so that he can attend to his business The person, who is badly knocked out nervously, generally has his or her troubles in the brain and not in the abdomen

Why Rest Did not Help —Many a woman when told that she needs a long rest, gets angry and says that she has had plenty of rest, and it has done her no good Often then especially after talking to the spouse, the physician will learn that although not working she really was not resting but was fretting fussing and working herself up into a terrible state of nerves Some persons seem to work harder while resting than they do when they are in the office Many have their brain teeming with all sorts of distressing ideas, worries and feelings of dissatisfaction Many continue to be undisciplined If they go on a trip, they take with them their cares and unhappinesses and perhaps an unloved and distressing spouse

The Tired Body and Nervous System Must Break Somewhere —Many persons with a nervous breakdown find it hard to understand why they should have gotten distressing symptoms as they did in some part

exactly what was the matter She would say it was whooping cough just because she had seen many a child with whooping cough before and knew the syndrome well Perhaps then she will grant the physician the right to make some diagnoses in just this way without the help of tests Unfortunately today even physicians worship tests so much that they as well as the patients refuse to accept an experienced consultant s opinion unless it is based on the results of tests

The Temptation to Give Diagnostic Placebos—Because it is such a difficult time consuming and often thankless and unremunerative task to get a nervous psychopathic or unintelligent woman to understand why she is ill and why she cannot promptly be made over into a well person the average physician is tempted to side step the problem and to get the woman out of his office quickly and in a happy mood simply by giving her some diagnostic placebo, some nice sounding word or set of words such as ptosis low blood pressure colitis spastic colon or low blood sugar which will satisfy her for a time and fill her with hope In this way he can get her out of the office in a few minutes Better yet if he diagnoses brucellosis that everyone else missed she will go away singing his praises loudly and telling all her friends that at last she has found the man who could locate the hidden cause of all her many symptoms

However the taking of this easy way out is unfortunate for all concerned If often indulged in the practice will soon make the physician lazy and a bit dishonest intellectually it will stop his mental growth Eventually he will come to believe his own buncombe and will not know that it is buncombe Besides it will not help the patient very long Often it will do her harm because now all her fear will be concentrated in some one organ which she feels is seriously diseased Now also she will keep going the rounds of physicians never listening to their opinion or advice but demanding that they concur in the diagnosis of brucellosis or colitis or what not and give her a cure for it

One of the greatest needs of American medicine today is the giving up of these diagnostic and therapeutic placebos Instead the patient must be made to see what the problem is Often she must be made to see that it is a life problem and hence always she must keep struggling to live more calmly, wisely and within her means of strength

Some day in the future many of the patients who are now given shots of this and that or operated on will be sent to a psychiatrist who will cure them after a few interviews

Need for Avoidance of Treating Unimportant Findings—One of the great things that a young physician has to learn as he grows older is to

would see that the woman is a fussbudget and puts $10 worth of energy into doing a job that is worth ten cents

Much illness is the price paid for civilization Often when a patient protests that he or she has not gotten anything out of the doctor's examination and counsel, it must be pointed out that he or she probably could be cured, if the doctor s prescription of rest could be filled, or if an easier and happier type of occupation could be obtained So long as the patient has to go on working and living in the environment, which has produced the nervous breakdown, it is almost impossible for the physician to do much in a helpful way

Patients Caught in a Trap —Quite a few persons, who are nervously ill, are really caught in some kind of an unhappy trap from which they cannot escape For instance a young woman may be supporting her aged parents, and this means that she cannot marry her beau or give up the uncongenial or overtaxing job in *factory* or *office* Perhaps the beau gets restless and decides to go elsewhere Under the circumstances there is little the physician can do to help her to sleep at night and to get peace of mind and health

Constitutional Inadequacy —It usually requires great tact and skill to get frail inadequate people to see why they have been ill so long, and why they probably never will be strong and well no matter how many medicines they take or how many operations they have performed Sometimes a frail little woman will admit that her mother before her was just as ailing and sickly as she is

At first sight it would seem a very discouraging thing to talk to a patient about constitutional inadequacy but if this is done with tact and kindliness and if the patient is intelligent enough to understand the situation great good can result The patient may then stop looking for a complete cure and will instead learn to live with what strength he or she has and will make every effort to conserve energy and not to waste it

The Need for Explaining How a Physician Can Diagnose Without Tests —Especially today when patients are often obsessed with the idea that it is only tests that count in the diagnosis it is well for the physician to insist that after many years of dealing with the sick he ought to be able to recognize many illnesses just from the story Perhaps he recognized the patient's disease the minute she told her story just because he had heard the tale hundreds of times before In trying to get a woman to understand this and today it is far from easy it may help to remind her that if she were to hear a child coughing in a particularly harsh and brassy way and then if the child whooped and vomited, she would know

he must disagree Perhaps he can point out that with the passage of time and the development of new symptoms or the failure of the patient to come to any bad end it has become obvious that the diagnosis made at home must have been wrong Often it should be pointed out that the diagnosis made at home while correct was insufficient to explain the symptoms For instance a woman with typical mucous colics due to anxiety over a sick child may have been told that she had amebiasis The physician may point out that although she probably did have some amebae in the bowel the fact that she was no better after these were killed off shows that they were not the cause of her troubles

The physician with a short temper must be particularly on his guard to keep from flaring up at the patient who questions his statements of fact or opinion, or who tries to argue some medical point or refuses a proffered treatment

Qualities Desirable in the Psychotherapist —Obviously the physician who expects to help nervous persons and to start them on the road to health must learn to be a good teacher and a good influencer and leader of men and women He must learn to talk well and interestingly and with simple speech He must learn to talk to lay persons without dragging in the long words that he has learned during his medical career He must remember that his patients will not understand these words and that they may get badly confused by his use of them Particularly helpful always will be the use of homely similes or little stories rather than of abstract and technical statements

Always there is great need for kindliness and sympathy The sick are often unreasonable because they are ill and the physician always must remember this and make allowances He must be patient The physician who really likes his patients can get along so easily with them he can influence them for their own good and when he makes mistakes they will forgive him because they like him

The wise physician will listen to his patients He will not only learn much that he needs to know about them and their illnesses but he will also learn much about medicine

On Beginning Psychotherapy —In many cases it is well to begin treatment by admitting that although the negative findings and lack of any signs of cancer or other serious disease have their delightful side they also have a very disappointing and baffling side and the physician can see clearly why the patient feels unhappy and somewhat outraged It would have been nice to find some disease which could have been cut out easily and cured in a moment but the physician did not expect to

avoid behaving like a poorly trained hound dog who goes running off after rabbits when his master wants him to follow the trail of a panther

I am reminded of an unhappy weepy woman of fifty who complained of symptoms which indicated a menopausal depression When her examination was finished she wailed because I would not do much in the way of treatment or promise her a cure I admitted that I felt hopeless about helping her She felt outraged because she said I had not found anything wrong with her My answer was that that was not the difficulty She had many things wrong, but they were not the cause of her symptoms First she had a basal metabolic rate averaging +25 per cent but her symptoms were not those of hyperthyroidism, and because a thyroidectomy done a year before had not helped her, it did not seem worthwhile to remove any more of the gland Second, the woman had some small stones lodged in the calices of both kidneys but, because they were not lowering the kidney function or producing any symptoms the urologist saw no reason for removing them Third she had two cholesterin stones floating around in a functioning gallbladder, but since she had no symptoms of cholecystitis, no surgeon wanted to remove the gallbladder Fourth she had a myomatous uterus but because it was not producing any symptoms, no one could see any sense in removing it Fifth, she had a high blood pressure but since it did not seem to be producing symptoms no one wanted to treat it strenuously Sixth she was in the menopause but since much treatment at home with hormones had not helped her I was not optimistic about further treatment Seventh she had an irritable bladder with a urethritis, grade 1, but the urologist feared that any treatment would make her worse than she was before so he would not start anything What was her real trouble? It was that her husband fed up with years of listening to her constant complaining, had gone off with a cheerful mistress I could not treat that

The Need for Answering All Questions and Objections —Often if a nervous woman is to be really helped the physician must have great patience with her and must keep answering her questions and meeting her objections without getting angry She cannot be expected to settle down to try to help herself until she is convinced that her troubles are functional The doctor must not try to overwhelm her with his authority but must talk to her like a friend

Always he will have to be gentle in combating her ideas about her diagnosis, and he will have to be kind and tactful in trying to combat the ideas that have been put into her head by previous consultants He must explain why with all due respect to them and their well known ability

One of the big things that a clinician can do is to recognize quickly the type of case in which the problem of psychotherapy is likely to be too difficult for him Such patients should be gotten quickly into the hands of a good psychiatrist who then can decide what is best to do He may decide also that the particular patient is beyond help or needs care in an institution

Methods of Treatment

Granting that a nervous patient is thought to be of the type that can be helped by simple psychotherapy and by an ordinary physician without special psychiatric training what is to be done? What instructions are to be given? Surely it will be useless to give the usual injunctions to snap out of it or forget it or stop worrying

Advice must be practical —Obviously advice must be practical and suited to the person s needs Often certain advice ordinarily good, would be useless in the particular case because the patient can not afford to take it he cannot take a vacation in the South or give up a trying job or turn over the care of aged parents to someone else Many sickly persons are caught in a trap from which neither they nor the physician can find any mode of escape With such persons it is heartless to express platitudes or to talk like Pollyanna who saw something to be glad about in everything

The Diagnosis Must Be Accepted —In the book Alcoholics Anonymous one reads that no dipsomaniac can be helped until he is willing to admit unreservedly before witnesses that he is an alcoholic and that he needs and wants help in the solving of his problem So long as he refuses to admit that alcohol has gotten the better of him and so long as he does not wish with all his heart and soul to be rid of his curse he cannot be helped

Similarly many neurotic persons cannot be helped until they are willing to admit that they are constitutionally frail that they have a poor nervous inheritance and that their diseases are due in large part to their own fretting fussing worrying and lack of discipline Then they must be willing to give up their placebos and buckle down to try to make themselves over into more successful persons Occasionally after they have pulled out and gotten well they write to say that they had a rebirth A woman of thirty five can be reminded that she probably has another thirty five years to live and surely she does not want to live all that time as she has been living Usually that makes her stop and think

find it, he looked carefully everywhere and he did not find it, and he now sees no sense in continuing to look for it He can tell of patients, who did go ahead and get the abdomen thoroughly explored and were not rewarded by the finding of any disease Other patients after suffering for years finally came to the end of their days, and then even a necropsy failed to show any cause for all their discomforts

The thing to do is to cheer up and learn to live with the handicap Perhaps with better living the discomfort will go away Sometimes the patient will admit that several consultants have all failed to find any organic disease and have diagnosed a neurosis Then it should be pointed out to the patient that perhaps these doctors were all correct, and that their advice should be given at least one short trial

A Good History May Cure—Not infrequently the physician can practically cure a neurosis by taking a history so good that the patient can see where his troubles came from and how they came Oftentimes the patient will then get up and say 'Yes you are right I can see now how I brought this all on myself and I can see that it is up to me to get rid of it' It is curious that often the most intelligent patients will have failed to see the connection between their illness and a great deal of anxiety and unhappiness

A Good Examination May Cure—Many patients are cured by a good examination which satisfies them and clears out their worries It is well for the physician to point to the high hemoglobin reading or the good blood count and especially a low blood sedimentation rate and all the other findings which indicate that the patient s health is good, and that there is nothing to worry about physically

Some Patients Are Probably Incurable—There are some persons who are probably incurable because they are too stupid psychopathic or opinionated ever to understand their problem or to be willing to take anyone s advice about it They never seem to gain any insight into the problem Such persons usually can be recognized easily as soon as they come in Many of them will not listen to what the physician tries to tell them, they keep breaking in to tell him what other physicians have prescribed Some have a low intelligence and many are probably somewhat insane

According to good psychiatrists many of the hypochondriacs are incurable Other patients are so extremely self centered and selfish that nothing can be done for them According to Ross and others psychotherapy is useless in many cases of melancholia, the condition just has to run its course

say to a patient, I think you have no heart disease but you had better go upstairs slowly, you had better make your will and here is a little digitalis No one so treated is likely to get well If a physician cannot be sure about the patient's heart he ought to call in a heart specialist who will come out flat footedly and positively say that the heart either is diseased or is not diseased at all

What Can the Patient Do About His Neurosis?

The first thing to do is to want to get well and want to so much as to be willing to make great efforts to get well and to break bad habits Next the patient should be honest and frank and tell the physician about all the factors that have made the neurosis and are keeping it up Too often he holds back the essential facts One of the most important things the patient should do is to follow Osler's great injunction to live life in day tight compartments to worry little about tomorrow and to waste no regrets over the mistakes and sorrows of the past Patients can be *reminded that hardly any of the disasters that they worried about so* terribly in the past ever came on them Many keep themselves ill by worry over the past and by reliving painful scenes

Austen Riggs had some good advice to give to worriers He said First ask yourself if the problem that is bothering you is yours to solve If it isn't and you cannot do anything about it then obviously you shouldn't spend three minutes on it Second if it is your problem ask yourself *if you can tackle it and solve it now If it can be tackled now* the thing to do is to get at it immediately If you cannot figure out what to do find an expert to help you Many a poor widow who has worried herself sick over some financial or other problem could have had it solved in a few minutes by consulting some wise lawyer banker or physician When expert advice is obtained it should be acted on Better by far is a poor decision than illness due to constant lack of one Once *a decision is made the subject should be closed unless some new in*formation has been obtained which requires that the docket be reopened

Indecision —One of the commonest causes of exhaustion in nervous and worrisome women is their inability ever to make a decision quickly and then to stick to it Often when a woman is made to admit that she really will never have the courage or the unkindness to get a divorce she still goes on day after day and night after night thinking of the problem She should *start teaching herself to make all small decisions* quickly and irrevocably Later perhaps she can make big ones quickly

Life Problems Must Be Studied.—Once a woman admits that her troubles probably are all functional, she can be shown how she should fight against certain bad habits of thought and behavior. She must be taught to stop wasting so much of her energy foolishly as she is now doing. Often it must be pointed out to her that nervousness and hypersensitiveness are not attributes that one need be ashamed of. Actually one might take pride in them because they are attributes of all those persons who accomplish much in this world, especially in the fields of art and literature.

Worrying and Fretting.—Every effort must be made to avoid worrying and fretting. In so many cases the patient's illness is due to a needless fear of disease. Some persons must be taught to go ahead and do things rather than to sit and try to figure them out. Many must be taught the value of acquiescence and of making the best of things. Others must be taught the great therapeutic value of work. It makes one forget one's troubles.

A Certain Amount of Psychoanalysis.—In some cases the physician must carry out a certain amount of psychoanalysis. It usually can be done in a few hours. Persons must be gotten to tell of feelings of inferiority, insecurity and craving for support. Many must be taught to stand on their own two feet. Occasionally a person must be shown that perhaps unconsciously he or she is using an illness to get out of work or to avoid the consequence of some misdeed. Others use illness to hang onto the affection of a parent, husband or brother. It should be pointed out to them that they could have more fun if they would live normally.

Mental Purgation.—Many a patient can be greatly helped by mental purgation by telling the story of mistakes and sins and sorrows and shame.

Psychotherapy Must Be Positive.—As Ross used to insist, once the physician has taken a good history and made a good examination and has decided that the patient's troubles are of neurotic origin, he should stop and refuse to repeat examinations. To go on examining implies doubt and this is fatal to success. The physician should be positive in his statements, if he is not, if he expresses doubt in word or deed, the patient will be full of worry again. Some physicians can never cure a neurosis because they cannot express themselves positively about anything. They always like to hedge and straddle and keep a line of retreat open. They are too worried about protecting their reputation and so arranging matters that if the patient should drop dead, they can say to the relatives "Well, you remember I warned you about that possibility." Some will

discipline They turn night into day they eat at any time, they often choose *poor friends* who have a bad influence on them they may drink one cup of coffee after another they may smoke one cigarette after another they may take too much alcohol and if they are given a sleeping tablet they soon are buying them by the hundred Whatever they do they do to excess and much of their illness is due to their bad habits and the resultant great strain on the body

Both men and women would be much better off, and they would keep the respect and love of a spouse if they would only learn to stand on their own feet and not keep constantly leaning on the other and demanding sympathy and mothering and help

Expecting Too Much Attention From Others—Many of the griefs of patients are due to their habit of expecting too much from others Many parents are greatly distressed because their children grow up and fail to show them the consideration and thoughtfulness that they think they should have One of the biggest lessons that one can learn in this world is that it is more blessed to give than to receive

Fussiness and a Desire for Attaining Perfection—Many women wear themselves out being too fussy and demanding too much perfection about the house Many of them demand too much of the husband Often what the neurotic sufferer needs to learn is What are the important things in this life As a physician once said to a fine man who was terribly fussy about certain things in his home you can force your wife to attend to these things for you but you are paying too heavily for it in the loss of her respect and love

The Hoarding or Budgeting of Energy—Probably many tired and nervous persons would soon get well if they could only learn not to waste their energy on things that do not count Many a woman needs to learn to run her home as her husband has to run his business He tries to get facts and then to act on them quickly dispassionately and finally She perhaps bases her actions mainly on emotions, prejudices and preconceptions of how the world should be run The husband if he is a good executive deals with the big problems and leaves all the rest to his trusted subordinates She often is unable to keep servants because she is constantly telling them every little thing to do and then doing it over after them

Excessive Shyness—Many persons are tired out at the end of the day because of the effort they make in just meeting people Probably here again the trouble is due mainly to too much concern over self and over the impression the shy one wants to make on the other person The

Avoid Tenseness—Much of the nervous misery of this world is produced by persons getting too tense and too hurried over what they are trying to do Often they are trying to do two or three things at a time and all of these in a rush Typical is the story of the bank teller, who admitted that whenever he saw more than six or seven persons in line in front of his cage he blew up and went to pieces

Internal Friction—So much of fatigue and illness seems to be produced by internal friction or conflict between two parts of the person ality between perhaps a good sensible, kindly and generous nature and perhaps a mean unpleasant mischievous trouble making, selfish, overly religious soul searching critical or crepe-hanging nature The constant warring that goes on between two such different personalities within the individual with perhaps contrition of the one over the escapades of the other or the constant searchings of conscience over imagined or petty sins wears the person out Riggs used to say so wisely to patients who were inclined to go on paralyzing debauches of conscience-searching one must take one s own essential decency for granted One can also point out to the soul searcher that he would not be doing what he is doing if he were not so impressed with his tremendous importance in the sight of God

Other persons who suffer terribly, are those with inferiority complexes, feelings of resentfulness of uncertainty of lack of appreciation and of disappointment over lack of achievement and success

Conflict With Others—Many persons get tired and worn out because of needless conflicts with others Some lose their temper and flare up and hurt the feelings of those about them and then they are uncomfortable or conscience smitten for a while Many nervous persons must be shown that they cannot afford to get angry and blow up in the way in which they are constantly doing It does them too much physical harm It brings hypertension migraine or indigestion The wise person lets others have their way in all unimportant matters if it will only enable him to have peace and quiet and lack of interference with the work he wants to do

Childish Behavior—Probably most of the troubles that make marriage difficult or unsatisfactory or which bring divorce are due to childish behavior If only both spouses would behave as dignified adults they would have no trouble Curiously many persons both men and women seem to feel no shame about displaying great childishness

The Lack of Discipline—The troubles of many neurotic and psychopathic persons are due largely to their bad habits and their lack of self-

women, must be induced to give up some of their activities outside of the home Some persons when they realize at last that they are constitutionally frail must give up some of their ambitions and must look for some less strenuous form of employment

One of the most valuable possessions that a chronically fatigued person can have is a wedge shaped pillow or a pillow with a firm back such as can be bought in a furniture store This will make sitting up in bed much more comfortable Another useful possession is a soft eye shade which will enable the patient to get a nap in the afternoon or to sleep late of a summer morning

On Talking a Woman Into Taking a Rest—Often before a tired mother can be induced to take a rest the physician must talk her into doing it First he must overcome her idea that if she rests she will fall down on her job Often it can be pointed out to her that she who so wants to be a good mother, is anything but that when she is so irritable and jumpy that she communicates her nervousness to her children Often she may punish them more because she was nervous than because they were naughty One must make the tired mother see that to neglect her household duties for a time is the most conscientious and honorable thing she can do It must be pointed out to her that her good health is one of her husband s greatest assets and that it will do him no good if she goes on and works herself into a hospital Often what holds her back from taking a rest is her pride she does not want to seem to have failed and she does not want to give her in laws the idea that she is a handicap to her husband

Often the husband also will have to be talked to so that he will not say or think anything which will cause the wife to stop resting Often for months before the woman breaks the husband has been watching anxiously the downward course of her strength and health and has been wishing that he could get her to rest The husband must remember that if his wife s mind is not at peace lying in bed will not help

Often when a physician says to a nervous woman that what she needs most is a month or two of mornings in bed her answer will be I could not stay in bed even one day I d be so restless I d go crazy The answer to this is that this very statement gives her away, it shows how badly she needs a rest She is keeping going on her nerve and is like the man who on the verge of delirium tremens takes another drink to steady up

A Rest Cure in a Sanatorium—A Weir Mitchell type of rest cure in a sanatorium with or without overfeeding can be a most helpful thera

normal man is not much concerned about such things, he is interested only in the other person and what he is saying With effort a man can overcome and grow out of much self consciousness and stage fright Sometimes a physician can help a shy woman with a bad inferiority complex by pointing out that she is really a fine person with good features and a fine body and has nothing to be ashamed about Oftentimes the bringing out of an inferiority complex was done by a sadistic brother a jealous stepmother or an ignorant husband, who realizing his mental or social inferiority, tried to pull his wife down to his level

The Unhappily Married—Many of the nervous patients the physician sees owe much of their trouble to an unhappy marriage In some cases the husband is a good provider and the only complaint brought against him is that he is not a lover or not attentive He does not do any of the little things that make a woman happy Often it turns out that the wife married him without love and never could develop it for him

In most such cases it helps greatly to get the woman to decide finally what she is going to do about the situation Usually she decides that she will stay in her home and then she must be exhorted to make the best of things So long as she keeps toying with the idea of divorce, she will not sleep she will not gain in weight, and she will be tired all the time

On Getting Rest

Especially when the patient's trouble is largely due to overwork or strain, to too long hours or to night work the most important part of the treatment must be rest Unfortunately, especially in the case of poor widows and mothers of several children it is hard to see how they can get it Then the physician must go over the problem with considerable care to see if in any way a breathing spell can be obtained Occasionally when a patient cannot get away for a real vacation, he or she can get health again by trying to live each day so as to put something into the bank of health something of the debt that has been run up through months or years of overwork or unwise or unhappy living

Sometimes better than a long vacation will be several short ones scattered through the year Many a tired mother, who cannot go on a vacation can get up in the morning feed husband and children and then go back to bed for the rest of the morning In bed she can do some mending writing or darning The important thing is that she will be stretched out and can relax Many of these persons both men and

therapist because, as Ross used to say, only one person at a time should administer this form of treatment to a patient

When women want to dawdle over their food it helps to have them eat by the clock and to insist that they get the food down within ten minutes. In some cases it helps to give from 10 to 15 units of insulin twenty minutes before the meal

Often during the rest cure the number of visitors must be limited and those persons who have a bad and tiring influence on the patient should be kept away. During such cures the foot of the bed should never be raised; there is no need for it, and it can only cause discomfort. At the start soporifics may have to be given to insure sleep and often they can help very greatly in the cure

Such a rest cure often can be helpful diagnostically because while the patient is being observed in the hospital much can be learned about her behavior and about the behavior and attitude of her relatives. Perhaps while in the hospital she will have one of her upsets and then much can be learned by the physician about this

Diet

As the physician grows in experience, he may find himself less inclined to hand out diet slips. More often he will feel like saying that with the patient's co-operation he would prefer to fit a diet. When trying to spare a patient's digestive tract, one is inclined to prescribe such baby foods as milk and eggs and then later it may be found that the patient was highly sensitive allergically to these two foods and all his or her trouble was due to eating them. Hence it is that many persons must be put for a time on a narrow elimination diet or must be made to keep a food diary to see if they can learn what the foods are which they must not eat

Many persons with a poor digestion and perhaps a short carnivorous type of bowel can be much helped by the prescription of a smooth type of diet from which much of the roughage is removed. They should take more meat, fish and eggs and less vegetables, salads and fruits. It would appear from man's early habits and the structure of his short digestive tract that he was designed to be more carnivorous than herbivorous

In many cases one can try a smooth low residue diet for a while during which time the patient must watch to see if any particular items cause distress. The essential thing is to keep a record of the unusual foods that were eaten immediately before an upset

peutic measure if the patient can afford it without worrying too much about the expense Unfortunately it is beyond financial reach of most patients who need it most Furthermore it is difficult to find a suitable place in which the cure can be carried out Most hospitals today are noisy places often situated on a busy street corner and devoted mainly to the needs of patients who are being operated on Sanatoria for the mentally disturbed are not entirely suitable a person who is not mentally upset does not want to be put with those who are upset, and she does not want the stigma that might go with a visit to such a hospital

Accordingly sometimes the only place in which a rest cure can be carried out is in the home of some devoted relative Usually it is hard to get a patient to rest in her own home especially if there are children about

The fattening of a thin tired little woman often helps but probably the rest along the way is more important than the fattening process Naturally if one hopes to overfeed a person who is finicky and has little appetite the food should be well prepared and attractively served No grease should be in sight and not too much food should be put on the plate at a time Preferably one course should be brought at a time No food or substance which the patient dislikes should be allowed on the tray Since the patient has little capacity for food or may feel full as soon as she starts eating the diet should consist mainly of concentrated foods which have a high caloric value Butter and cream should be tucked away in other foods such as soups purees mashed potatoes, cereals and puddings The roughage can be largely left off for a time and constipation if it comes can be combated with enemas of warm physiological saline solution

Many patients fear that they will not be able to digest food eaten under duress but actually if the patient's mind is at peace, usually she can digest what is eaten and she can gain in weight When a woman who is taking more than 3 000 calories a day does not gain it is highly probable that her mind is fretting over something

In handling such patients it is a tremendous help to have an able nurse in charge who is cheerful, dynamic tactful and friendly She will often succeed in getting the patient to eat she will help cure her of some bad nervous habits and she will help her past some discouragements and set backs Often she will find out what are the things which are worrying or fretting the patient and she will find out what her worst sins of commission are The nurse should not try actively to be a psycho-

between meals Hot cakes and waffles might not be bad, if they were well chewed and not eaten with much syrup Fried foods are not bad if they are properly fried that is, totally immersed in fat at the right temperature

Avoid eating when in a rush, when very tired or when mentally upset Family rows should be held away from the table Chewing gum may cause distress because air is swallowed with the saliva Digestion is greatly helped by a good chewing surface If there are gaps in your teeth have your dentist fill them with bridges The taking of purgatives should be avoided as they sometimes cause flatulence and abdominal distress

For Breakfast

You may have orange juice or grapefruit (avoid the fiber in the compartments) Cantaloupe and other melons are inadvisable Coffee if desired is allowed in moderation it sometimes causes flatulence If you are sensitive to caffeine, try Kaffee hag sanka coffee or postum You may have chocolate and cocoa (if they are found to agree) or tea, one or two eggs with bacon or ham white bread toast or zwieback, with butter, any smooth mush such as farina cream of-wheat corn meal or rolled oats, also puffed cereals or cornflakes Shredded wheat biscuits and other coarse breakfast foods are not allowed Bran must not be used in any form Graham bread is permitted but not the coarser whole wheat breads

For Lunch and Dinner

In fruit cocktails avoid the pieces of orange and pineapple Broths, bouillon cream soups and chowder are allowed also meat fish chicken, eggs and oysters Eat no smoked fish or pork Eat crab and lobster only if you know that they agree with you

Bread and butter are allowed also hot biscuits if made small so as to consist mainly of crust You may have potatoes (baked mashed hash brown or French fried) rice sweet potatoes hominy tomatoes (stewed strained and thickened with cracker or bread crumbs) asparagus tips carrots turnips, creamed spinach zucchini (an Italian squash) Italian pastes such as noodles, macaroni and spaghetti (cooked soft) and purees of peas lentils lima beans or artichoke hearts there are practically no other vegetables that can be pureed to advantage Sweet corn may be used only if passed through a colander Tender varieties of string beans may be eaten They can be used in salads

No salad should be taken at first Later you may try lettuce with tomato jelly, hard boiled egg, ripe tomato string beans pears peaches

From many experiments on animals it seems probable that a diet low in residue will produce an intestinal content which can travel most easily down the bowel even when the gradient of forces is poor Perhaps the man with a flabby digestive tract or one with irritated, narrowed or, in a way reversed stretches should avoid eating cellulose rich food for much the same reason that he will avoid putting paper, bits of wood or cotton down a drain that has a poor gradient or somewhere in its course an uphill stretch or a narrow place

Perhaps another reason for the efficiency of a low roughage diet in many cases is that the human intestine has no ferment for the digestion of cellulose Actually, it is hard to explain why man is able to handle vegetables and salad and fruit as well as he does

The Smooth Diet—Following is a prescription for a smooth type of diet such as is helpful in many cases of functional indigestion This diet is based not only on practical experience but on a number of scientific principles We have no ferment in the digestive tract which will dissolve cellulose that is the fibrous part of vegetables and fruits Most of this material is largely indigestible and if we eat much of it, we throw a heavy burden on the bowel This fiber interferes with the digestion of starches and predisposes to flatulence

If there happen to be narrow or spasmodically contracted places in the bowel the fiber may cause clogging and back pressure The ideal diet in such conditions is one which leaves only a small liquid residue which can trickle through the poorly functioning segments of bowel and in this way bring relief This diet is indicated also when the bowel is irritable, overly active and overly responsive to every stimulus

It should be tried out faithfully at first and then, if it works well, other foods may be experimented with one at a time If you have learned by experience that some of the foods allowed on this list are hurtful to you leave them alone

If you are to give this diet a fair trial, eat no coarse foods with fiber, skins, seeds or gristle Avoid salads with celery, cucumbers and pineapple, also many of the green vegetables, raisins, berries, jams full of seeds, nuts and many of the raw fruits Beans, cabbage, onions, peppers, melons, cucumbers, radishes and peanuts are notoriously gassy

Pureed vegetables and fruits can be obtained in cans

If you are living in a hotel or boarding house, you can follow this diet by avoiding the forbidden foods and eating more of the digestible ones which are put before you

Avoid sugar in concentrated form and take no candy or other foods

on the tray that disgusts the patient Some women who have a tendency to pick at their food should be made to eat rapidly within ten to fifteen minutes by the clock

Some women can take with advantage a glass of milk with cream in the middle of the morning and the afternoon but if these extra feedings interfere too much with appetite they should be stopped

The patient should be in bed during the morning but may get up and move around in the afternoon

Mental peace is essential Patients who are worrying fretting or unhappy or wondering what a husband or lover is doing will not gain

If there should be any constipation it should be relieved with enemas of warm physiological saline solution

Many persons worry for fear that so much food eaten under duress will not be digested Actually experience shows that it can be digested Some persons on an overfeeding cure in a hospital will gain a pound or more a day

Some physicians are afraid of giving so much food and lead the patient into an overfeeding cure gradually but this does not seem to be necessary One might as well begin with a full diet of 3 000 calories or more Occasionally because of distress there may have to be a letup for a day or two but then the full diet should be given promptly again

The patient should be weighed each day so as to keep up her interest and enthusiasm

If any food is found to disagree or to give the patient mental nausea it should be proscribed

If the patient can afford it and a good sensible optimistic and friendly nurse can be obtained she can help greatly especially in tiding the patient over the first few hard and perhaps discouraging days

Physical Therapy

During the process of a rest cure with overfeeding an able physical therapist can be of great help not only in toning up the woman's flabby muscles but in keeping up her morale If the patient is of the type who enjoys massage she will look forward to her hour of massage and will feel happy that something is being done for her

Treatment With Drugs

In many physicians offices the custom today is to give phenobarbital to all nervous worried depressed or uncomfortable patients In many

or chopped apple Mayonnaise and French dressing are allowed Potato salad without onions is permitted

For Dessert

Take simple puddings, custards ice cream, desserts made of gelatin, plain cake and canned or stewed fruits particularly pears and peaches Cottage cheese is permissible other cheeses may cause trouble The filling of apple, peach, pear, apricot custard or lemon cream pie may be eaten

In case of constipation stewed fruit may be taken once or twice a day In winter, dried, pared fruit may be used for stewing The small canned figs are probably the most laxative of fruits, and their seeds will do no harm Prunes may also be helpful They should be cooked slowly until they almost go to pieces Apple sauce is more palatable if made from unpared and uncored apples it should be strained It can also be cooked with tapioca or sago Blackberries and loganberries can be stewed and strained, and the sweetened juice thickened with cornstarch This makes a delicious dish with the full flavor of the berries Later you may try uncooked fully ripe pears and peaches Bananas are digestible when cooked or when uncooked if fully ripe

Make no effort to drink water Be guided by your thirst Avoid excessive use of salt, pepper or other seasoning

If you wish to gain in weight, eat as much cream, butter, fat and starch as you can If you wish to lose weight or to stay thin, live largely on the allowed vegetables fruits and salads with a moderate amount of meat, fish or chicken each day also a glass of milk and an egg

Overfeeding —When a woman is tired and much reduced in weight it may help to fatten her and what with the rest cure and the fattening she may get to feel and look like a new woman The best place in which to give a rest cure is a good sanatorium where good food and quiet and rest can be secured Unfortunately in recent years with the shortage of hospitals and nurses such ideal conditions are hard to find

The diet should be smooth and have a high caloric content Naturally, when a patient has not much appetite one wants to give concentrated foods In addition to the smooth diet one must give as much cream and butter as can be taken without disgust or nausea These fats should be hidden away in cream soups purées mashed potatoes, puddings and scrambled eggs Cream can be added to coffee or chocolate or milk and it can be put on mush and stewed fruit

Naturally the patient's tray should be as attractive as possible Preferably one dish at a time should be presented, and nothing should be put

so afraid of prescribing them as some physicians are I have seen very few examples of addiction and in all those cases the patient was a psychopath or undisciplined person to begin with and that is why he or she used so much of the drug In these cases my impression was that the addiction was not like that to morphine because the patient could easily be taken off the drug without being given symptoms of withdrawal The only complaint then was, what will I use now in order to get some sleep

One person, a highly intelligent man for over ten years now has taken from 10 to 12 grains (0 65 to 0 78 gm) of nembutal a day Without it he used to be a nervous wreck going sometimes into a psychopathic hospital for relief but since taking it he has been a successful and happy professional man He shows no signs to suggest that the drug has done him any harm Instead of dulling his mind the nembutal seems greatly to improve his faculties by setting him free from anxieties and distresses

Many physicians give strychnine to nervous patients but this seems to be unwise These patients are already on edge and it must be remembered that the only action of strychnine is to exaggerate their reflexes.

Most nervous patients want a nerve tonic of some kind and although it is doubtful if there is such a thing most physicians give something Especially if the patient has been living on a scanty and somewhat insufficient diet it may help to give daily doses of a syrup of B complex Women who tend to have a low hemoglobin reading year in and year out may feel better for taking some iron In such cases liver extract is not the drug that is indicated this is more likely to be of use in the primary macrocytic anemias

Years ago physicians gave bitters to many patients but there is no good evidence that they ever did any good and the practice now is being largely given up Occasionally on a day when the patient feels low and depressed a dose of benzedrine or desoxin may help but it is always questionable if one should whip a tired horse

Years ago many physicians gave pepsin and pancreatin to patients with indigestion but as Fermi and Ivy have shown these substances have but little influence on digestion unless perhaps given in large amounts Some physicians use bismuth as a sedative to the digestive tract and especially when there is some diarrhea it may be helpful It should be given in teaspoonful doses in order to get some effect The subgallate may be particularly useful in cases of diarrhea

cases, of course this treatment does help but in others, and especially in the case of patients who are depressed it does not seem to be a logical form of treatment At times when a woman is jittery and ready to fly to pieces , she can be helped by a sedative but it hardly seems wise to give her a depressant drug three times a day day in and day out Many patients are given bromides and in some cases this drug accumulates in the body until it produces a mild psychosis Always when a physician takes over the care of a neurotic woman it is well to find out how much bromide she is taking and if she is taking too much, it is well to have the laboratory measure the amount of bromide radical in the blood

When a patient is suffering greatly from insomnia it is usually well to let him or her have a sedative at night Often the most curative measure that a physician can use in the case of a nervous breakdown is a sedative that will enable the patient to sleep In this way one can break into a vicious circle Unfortunately the less the patient sleeps one night the less he is likely to sleep the next

The physician should find out what type of insomnia the patient has Many persons find it hard to get to sleep but once they do drop off they are safe for the rest of the night For them a short-acting drug such as bromural (a monobrom iso-valeryl urea) is best They do not need a long acting drug like phenobarbital

Other persons on going to bed go to sleep all right but they wake soon afterward or perhaps at four o clock in the morning and then cannot get to sleep again They need a sedative that will act for eight hours or if they wake only at four or five o clock they can use bromural which has so short an action that they can get up at seven in the morning with a clear head

Other patients go to sleep but they are constantly waking a bit or tossing about or drowsing off again and as a result they get but little rest They can be helped greatly by taking a mild drug such as adalin or carbromal One or two tablets of this drug may make all the difference between a restful night and a restless tiring one Seconal is a drug which often works well for nervous persons It can be given in doses of ¾ or 1½ grain (0 05 to 0 1 gm)

Some jittery and highly apprehensive or somewhat depressed persons can be made over into comfortable hard working and sensible members of the community so long as they take some pentobarbital sodium (nembutal) by day and by night In some of these cases this drug appears to have an effect which the other barbiturates do not have

After forty years of watching patients take sedatives I do not feel

miracle of healing accomplished by the removal of focal infections there are scores of failures to accomplish anything The wise physician will pick for the the strenuous treatment of foci of infection only those patients who have some disease which he thinks is likely to be helped by this

Avoidance of Operations on Nervous Patients

The physician who has not a wide acquaintance with functional troubles the man who does not know constitutional inadequacy well and who is not able to recognize quickly the psychoneurotic or the psychotic patient or the man who does not take a good enough history so that he learns of the terrible mental problems of some of his patients or the man who has great faith in surgery and is convinced that if he goes at things strenuously enough, he can cure anyone such a physician will order an operation on many persons who should not have it Often he will grasp at straws hoping for instance that the removal of a small myoma of the uterus will make a tired neurotic frail woman over into a strong one Actually myomas of the uterus should be left alone unless they are growing rapidly or causing the woman to flood so that she cannot regenerate lost hemoglobin fast enough Occasionally a myoma should be removed because it is very large Today thousands of women are submitting to hysterectomy because of a small myoma and the physician s warning that it may become malignant Actually from my experience this warning does not appear to be justified I cannot remember when I have heard of a neglected myoma becoming cancerous or sarcomatous

Many psychoneurotic and constitutionally inadequate persons still are being advised to part with a perfectly harmless and normal appendix The wise physician will not diagnose chronic appendicitis unless the patient recently has had one or more painful upsets that seemed definitely to be attacks of acute appendicitis Many patients are also now parting with a normal gallbladder because it was reported by the roentgenologist as emptying slowly Actually it really was refilling with dye which was reabsorbed from the jejunum

Fortunately most surgeons have by now learned the unwisdom of performing gastroenterostomy with the idea of helping an asthenic or neurotic patient Most surgeons also have given up the practice of stitching up the right kidney when it is low lying If the patient s pain were due to back pressure from a kink in the ureter one would expect

One of the commonest drugs given today to patients with functional indigestion is belladonna The idea is that most of their troubles are due to spasm in the muscle of the digestive tract It is doubtful if this thesis is often correct The trouble would seem to be due more often to a failure of contractions to move normally and peristaltically down the gut There are cases in which the giving of belladonna or atropine or novatropine seems to do some good but with physiological doses, which are likely to have some effect on the bowel, there are unpleasant by-effects on the eyes and on the salivary glands Many physicians have of late substituted trasentin and other new drugs but, I fear, without any startling results

Management of Focal Infection

It is doubtful if focal infection accounts for many cases of nervous breakdown and fatigue However when one is trying to improve the health of the patient, it is well to check the teeth and to remove those that have abscesses at their roots In many cases of older persons it is most unwise to remove the teeth because, especially if this means that the patient must get plates it may make a wreck out of him or her The physician should remember that many a highly sensitive woman who gags whenever she tries to brush her back teeth will find it very hard to adjust to wearing plates Hence she should be encouraged to keep her teeth as long as possible

I doubt if the removal of tonsils from older patients does much good In the case of younger people the tonsils should be removed, if they are full of pus and if the patient has frequent colds and sore throats

Many persons go to the gastroenterologist complaining of what they think is sinusitis and stating their belief that the material which goes down the nasopharynx is poisoning the stomach They think they can be made well by having the sinus condition cleared up There are a few cases in which the making of an antral window will improve the patient's health and apparently relieve indigestion In most cases the patient who thinks he or she is suffering from sinusitis has not any sign of pus in the nose What is present is a hypersecretion of the glands in the nasal mucosa and the material that goes down the nasopharynx is not pus but a jelly-like material which if swallowed cannot possibly do any harm The wise and conscientious nose specialist will not do any operating on the noses of these people

The point that every physician should remember is that for one

a benign ulcer on the duodenal side If this were true in 100 per cent *of cases all would be delightful but unfortunately there are a few* cases of early gastric cancer associated with hyperacidity and a few cases of duodenal ulcer associated with anacidity at least to the usual single test with an Ewald meal and it is this slight chance for error that causes the wise physician to refuse to risk a man s life on one report from a laboratory

In most cases gastric analysis fails to help simply because the report that comes back from the laboratory is that of some noncommittal figure such as 25 units of free acid which might go with anything Because of such drawbacks many a wise gastroenterologist today seldom orders a gastric analysis and then only because he wants an answer to a specific question such as Has this man with a somewhat hyperchromic change in his erythrocytes an achylia If so then he can have a primary anemia *now or later*

If gastric analysis is so often disappointing why is it that way? First in most cases of indigestion the trouble is a functional one arising probably in the nervous system in other words the digestive tract is not at fault and should be normal Second when there is some disturbance of function in the tract it is probably more likely to be in the bowel or gallbladder than in the stomach Third when there is some disease in the stomach such as ulcer gastritis or cancer little change in gastric acidity can be expected until a large part of the mucosa has been de stroyed injured or thrown out of action Fourth even when much of the gastric mucosa is not functioning as when the surgeon has removed two thirds of it the acidity of the gastric juice may not be much lowered if at all because the parietal cells that remain continue to secrete hydro *chloric acid in the usual concentration* Fifth *the laboratory report gives* the acidity of a variable mixture of several unknowns of saliva food acid gastric juice and alkaline diluents some arising in certain cells of the gastric mucosa and others supplied by juices regurgitated from the duodenum The wonder is that the algebraic sum of the acidities and alkalinities in this complex mixture should ever have been expected to tell much of diagnostic value

Furthermore if the pylorus should happen to be somewhat blocked by an ulcer so that the stomach empties slowly much hydrochloric acid may accumulate but then it will be so diluted with water and food that *the report of the laboratory* will indicate the presence of subacidity *In* such case high chloride values may throw light on the true nature of the situation

to find the pelvis of the kidney somewhat dilated, and usually one does not find this Furthermore if the pain were coming from the kidney the woman should be comfortable in bed and usually she is not Fortunately today most surgeons have given up the custom of suspending the retroverted uterus

Disturbances in Gastric Secretion

Years ago when the stomach tube and gastric analysis came into wide spread use variations in the amount and acidity of the gastric juice were looked on as diseases and treated as such Hypersecretion hyperacidity subacidity and achlorhydria were all treated with medicine diet and perhaps intragastric faradization

Then came the roentgen rays and the discovery that hyperacidity and hypersecretion often are associated with duodenal ulcer and pyloric stenosis later came the discoveries that (1) achylia goes sometimes with primary anemias (2) the incidence of achlorhydria increases with age much as does baldness, and (3) atrophic gastritis with low acidity is common

Today the well educated gastroenterologist does not think of treating disturbances in gastric secretion per se He knows that commonly they do not produce symptoms and can be disregarded When they are associated with symptoms he looks beyond the disturbance in function for some basic condition, such as ulcer, cancer gastritis or neurosis and treats that

Clinical Significance and Value of Gastric Analysis

The last thirty years have seen the publication of a tremendous amount of work on gastric secretion work done in an effort to make gastric analysis of more value to the clinician Unfortunately, in spite of every refinement of technic that has been suggested in most cases of indigestion gastric analysis still fails to settle the diagnosis A certain report may add considerable support to the physician's hunch or to the roentgenologist's diagnosis but it often fails to help at all and it may even lead everyone astray

For instance an elderly physician was found to have an obstructing lesion at the pylorus, a laboratory report of anacidity or marked subacidity should have meant that the trouble was on the gastric side and perhaps carcinomatous, while a report of hyperacidity should have meant

a benign ulcer on the duodenal side If this were true in 100 per cent of cases all would be delightful but unfortunately there are a few cases of early gastric cancer associated with hyperacidity and a few cases of duodenal ulcer associated with anacidity, at least to the usual single test with an Ewald meal, and it is this slight chance for error that causes the wise physician to refuse to risk a man's life on one report from a laboratory

In most cases gastric analysis fails to help simply because the report that comes back from the laboratory is that of some noncommittal figure such as 5 units of free acid which might go with anything Because of such drawbacks many a wise gastroenterologist today seldom orders a gastric analysis and then only because he wants an answer to a specific question such as Has this man with a somewhat hyperchromic change in his erythrocytes an achylia If so then he can have a primary anemia now or later

If gastric analysis is so often disappointing why is it that way? First in most cases of indigestion the trouble is a functional one arising probably in the nervous system in other words the digestive tract is not at fault and should be normal Second when there is some disturbance of function in the tract it is probably more likely to be in the bowel or gallbladder than in the stomach Third when there is some disease in the stomach such as ulcer gastritis or cancer little change in gastric acidity can be expected until a large part of the mucosa has been destroyed injured or thrown out of action Fourth, even when much of the gastric mucosa is not functioning as when the surgeon has removed two thirds of it the acidity of the gastric juice may not be much lowered if at all because the parietal cells that remain continue to secrete hydrochloric acid in the usual concentration Fifth the laboratory report gives the acidity of a variable mixture of several unknowns of saliva food acid gastric juice and alkaline diluents some arising in certain cells of the gastric mucosa and others supplied by juices regurgitated from the duodenum The wonder is that the algebraic sum of the acidities and alkalinities in this complex mixture should ever have been expected to tell much of diagnostic value

Furthermore if the pylorus should happen to be somewhat blocked by an ulcer so that the stomach empties slowly much hydrochloric acid may accumulate but then it will be so diluted with water and food that the report of the laboratory will indicate the presence of subacidity In such case high chloride values may throw light on the true nature of the situation

New Methods of Analysis

It is possible that an indicator method of gastric analysis, such as that developed by Wilhelmj[1] (1936) would be more helpful in diagnosis and prognosis. In such a method the addition of a dye or indicator to a meal of dilute Liebig's extract enables the laboratory worker to report the amounts of acid and alkaline juices secreted by the stomach in half-hourly intervals together with the total amount of acid secreted in, let us say, two hours. In spite of the decided promise of this method it has not yet been adopted into clinical practice.

Two modifications of the old method of gastric analysis have become almost routine in many laboratories; they are the fractional method and the fractional method after histamine. The popularity of these methods persists in spite of the fact that except in the field of primary anemia they have not been of much use to the clinician. At first it was thought that certain plotted curves of secretion indicated the presence of ulcer, but soon these curves were found in the cases of any number of tense nervous persons without ulcer. Similarly it was found with histamine that the distribution polygons of data obtained from patients with ulcer so closely overlap the distribution polygons made from data obtained from "normal" persons that the new method is no more useful in diagnosing ulcer than was the old one [see Comfort and Osterberg[2] (1931) and Paul M. Glenn[3] (1946)].

Actually, except in cases of puzzling anemia, one might expect gastric analysis after histamine to be of less value than the analysis after a meal of some kind because the histaminic stimulus is an abnormal one which tends to make the parietal cells secrete to the limit of their ability. Perhaps it is a disadvantage to get figures which represent the activity of the glands pushed up against a sort of ceiling. An advantage, of course, with the histamine test is that one can get pure juice unmixed with food, and one can measure the amount of juice secreted in a given time.

Pepsin.—Vanzant, Osterberg, Alvarez, Judd and Rivers[4] (1936) studied the pepsin in the gastric juice of some 1,800 persons to see if the measurement of this substance would have diagnostic or prognostic values greater than those derived from the study of hydrochloric acid, but they were disappointed. In cases of duodenal ulcer the concentration of pepsin was much higher than normal and it was still higher with acute ulcers and severe symptoms, but unfortunately the individual variability in pepsin readings is so large and the overlapping of distribu-

tions from normal and diseased persons so great that estimations of this ferment can hardly have much diagnostic or prognostic value

Figures for pH Would Be Better than "Units" of Acidity.—One difficulty with gastric analysis as now carried out, may be found in the fact that still today physicians cling to an antiquated method of reporting gastric acidity in terms of arbitrary units of "free" and "total" acid terms which are not very satisfying to the modern chemist. As Northrop once pointed out pH values should be more helpful to the clinician, if only because they would tell him what he often most wants to know, as after operations for ulcer, and this is is there enough acid present to activate pepsin effectively and dangerously?

A Better Method of Recording Units of Acid.—If physicians will persist in using the old unit method of notation they might help themselves greatly by following the technic of Vanzant, Alvarez, Berkson and Eusterman[6] (1933) and expressing each report from the laboratory of free or total acidity as a difference plus or minus from the normal (mode) for the individual's age and sex. Such figures can then easily be averaged so as to show even small differences in data from groups of patients with gastric or duodenal ulcer or even with ulcer as located in the several parts of the stomach. The old method of classifying the figures from two groups of patients with different diseases as normal hypo-acid hyperacid and anacid is so cumbersome that small differences in data from two groups of patients cannot possibly be detected with it.

In order to get the necessary standards of normal from which the differences in individual data could be read much as in the case of reports of basal metabolism Vanzant, Alvarez, Lusterman, Dunn and Berkson[7] (1932) analyzed data from 3 381 persons without demonstrable organic disease in stomach or body. On plotting the averages it was found that the most commonly observed or modal figure for free acid for men ranged from 45 to 50 units during the years from 20 to 40. After this the curve fell off to 30 or 35 units around the age of 60 years. In women the mode remained practically constant about 35 units between the ages of 20 and 60 years. The modal total acidity for men ranged from 66 units at the age of 20 years down to 56 units after the age of 65 years. In the case of women the figure remained about 51 units throughout adult life.

With the new technic it was shown clearly that the presence of gastric ulcer especially in the upper third of the stomach lowers gastric acidity while the presence of cholecystitis or the removal of the gall bladder has no clear cut influence.

Studies of the Fasting or Night Secretion

Studies of the fasting secretion of the stomach have been made, but they have resulted in figures that could not be used with certainty in diagnosis. Studies of late evening hypersecretion will be discussed in the sections on hypersecretion.

Mucus and Blood

The finding in the gastric juice of much mucus and especially of mucus of certain types may have some diagnostic value. It suggests the presence of gastritis or possibly of some disease in the brain affecting the nuclei of the vagus or glossopharyngeal nerves.

The finding of blood, if not due to traumatization with the tube, will suggest the presence of an ulcer or cancer. An able laboratory girl sometimes will make the diagnosis of a carcinoma near the cardia by noting a foul odor on the tube as it is withdrawn.

Gastric Stasis

Often the laboratory worker will report slight degrees of gastric stasis before the roentgenologist does, and this finding may be helpful to the clinician.

Achlorhydria with Duodenal Ulcer

Occasionally the discovery of achlorhydria or a marked subacidity in the case of a person past middle age with a roentgenological report of duodenal ulcer can warn the physician that what was seen in the duodenum was probably only an old scar and that further search must be made for the cause of the symptoms. There may be a carcinoma in stomach, pancreas or lung, or there may be disease in the gallbladder, or there may be a hiatus hernia or a failing heart.

Value of Gastric Analysis in Prognosis

At first glance one thinks of using gastric analysis in the making of a diagnosis and forgets how valuable it would be, if some modification

could ever be found, which would give us physicians information of value in prognosis What the gastroenterologist wants most to know in every case of severe duodenal ulcer is if he has the individual operated on will he remain well or will he soon be back with a new ulcer?

Many physicians and surgeons assume today that the man with a high gastric acidity will be the one who returns with a new ulcer, but the only follow up study I know of designed to get an answer to this question did not bear out this hunch Vanzant Alvarez Berkson and Lusterman[6] (1933) found, to be sure that in cases of duodenal ulcer the higher acid values are reported usually for the type of patient with the severest symptoms but there was so much overlapping of the polygons representing data from the two groups of those who remained well for a few years after operation and those who did not that no single reading in any individual case could be given any prognostic value The same was found true for pepsin values by Vanzant Osterberg Alvarez Judd and Rivers[4] (1936)

Perhaps more helpful diagnostically and prognostically would be a study of the amounts of acid or juice secreted after 10 o clock at night Continued night secretion after the stomach is empty appears to be common in cases of duodenal ulcer and it may be characteristic of this disease This observation has been made by a number of men but questioned of late by Sandweiss and his co-workers[8] (1946) The work of Lester Dragstedt[9,10] with double vagotomy above the diaphragm adds support to the view that this troublesome and dangerous night secretion is produced largely by stimuli coming down from a restless brain along the vagus nerves

Hyperacidity

As Carlson pointed out years ago there is probably no such thing as a true hyperacidity that is with a secretion of acid of more than 0 5 per cent or a pH lower than 1 0 Usually with so-called hyperacidity one finds in the stomach an acidity around 0 25 per cent As Apperly and Cameron (1923) showed if one puts 250 c c of 0 4 per cent hydrochloric acid into the stomach of a normal person it is soon neutralized Actually, when one finds persistently high acid values one must suspect not so much that the gastric glands are abnormal or that they are secreting an abnormally concentrated acid but that they are working overtime due to some abnormal stimulus or that one of the neutralizing mechanisms has broken down The two commonest causes for hyper

acidity are probably (1) a tense nervous system with a certain type of inheritance and (2) a duodenal ulcer. High acidities have been noted also with exophthalmic goiter.

Many years ago, when it was first discovered, hyperacidity was thought to be a disease in itself; today it is looked upon more as a symptom. Furthermore it is recognized that a man with a free acid of 90 units can be perfectly comfortable all his life and hence without need for any treatment. As is pointed out in the section on heartburn many of the patients who are sure they have a most acid stomach, really have a low acidity and some few have no acid at all.

Treatment.—Naturally, many persons with hyperacidity and distress with it need to take antacids of some type. The tendency today is to use less sodium bicarbonate because of its ability to produce alkalosis, and to take one of the antacids made from aluminum hydroxide.

In years past some authorities thought that meat should not be given to persons with hyperacidity because this would stimulate the production of acid, but others advised that meat be given to combine with the acid. Most writers have warned against the use of soups which should stimulate the acid without combining to any great extent with it. According to Babkin,[11] fish and vegetable juices are strong stimulants to secretion. Ivy and his colleagues found coffee to be a strong stimulant.

Some men have advised the giving of fat to depress the secretion of acid, while others have advised against this because fats tend to slow the emptying of the stomach and this will keep the acid for a longer time in contact with the gastric mucosa. When authorities are in such disagreement it is usually best not to prescribe much. Alcoholic drinks, tobacco and perhaps spices can also increase the secretion of acid.

Attempts Made to Put a Stop to the Secretion of Acid in the Stomach.—Much work has been done in the hope of finding some way of stopping the secretion of acid in the gastric glands. Surgeons have shown that the removal of a large portion of the lower end of the stomach usually will lessen the amount of acid titrable in the gastric juice, but this appears now to be due not so much to a secretion of a weaker acid as to the more rapid emptying of the stomach which shortens the gastric phase of secretion. In addition of course there is the diminution in the area of mucosa containing acid-forming glands. What secretion there is appears to be just as strongly acid as it ever was (Comfort[1], 1934) and hence ulcers sometimes still form in the jejunum.

Attempts have been made to remove only the acid-secreting upper part of the stomach, but the technical problems appear to have been too

great Many men hoped that the removal of the pars pylorica would get rid of some stimulating hormone such as that postulated by Edkins, but this theory has not proved to be correct

Years ago Hartzell and others showed that by sectioning the vagus nerves in the thorax of dogs one could greatly lower gastric acidity Unfortunately if even a few fibers of one nerve were left the acidity usually did not drop at all Later after two or three years Vanzant re examined some of Hartzell s dogs and found that in most of them the acid secretion had to a large extent returned With Frank Mann she cut the vagus nerves in several more dogs and after two or three years found that also in some of them the secretion of acid had returned The gastric glands of these dogs still responded poorly to histamine (Vanzant 1947)

In the last few years Lester Dragstedt and other surgeons[9,10] have been cutting the vagus nerves above the diaphragm in men with ulcer and have found that usually the acid drops to a low level and the ulcer heals Cases however have been reported in which there was no decided drop, but it is possible that in these cases all branches of the vagus nerves were not cut It is still too early to know whether this operation is going to be the answer to the problem of treating ulcer

Many years ago Wilms (1916), Bruegel (1917) and Bryan and Dormody (19 1) were treating duodenal ulcer with roentgen rays and were noting a temporary lowering of the gastric acidity More recently Walter Palmer and his colleagues have used this method with encouraging results.

Hypersecretion

A slight degree of hypersecretion often is associated with hyperacidity and is perhaps somewhat responsible for it In a study made by Vanzant Alvarez, Berkson and Eusterman[58] (1933) it was found that in a group of patients with duodenal ulcer the amount of gastric juice removed after an Ewald meal averaged 10 c c more than in normal persons. This figure would have been much higher if those cases, in which there was pyloric obstruction had not been excluded

Some students of the subject have thought that hypersecretion is more significant in a diagnostic way than is hyperacidity There are reasons for believing that hypersecretion in the hours between 10 p m and 2 a m is common in cases of duodenal ulcer and that the presence then in stomach and duodenum of poorly buffered acid has much to do

with keeping the ulcer from healing. As already noted, in many cases this continued secretion in the absence of food probably is due to nervous tension and to a stream of stimuli coming down the vagus nerves from an overly active brain. That parts of the brains of persons with ulcer often remain overactive at night is shown by the fact that most such persons are restless sleepers. At night they make so much noise tossing about or grinding teeth or talking that the wife often wishes she could sleep in another room.

There are doubtless many nervous persons whose stomach secretes to excess especially at night but who do not know about it or do not have any reason to complain of it. So long as the acid juice remains in the largely insensitive stomach the person cannot become conscious of its presence. It is only when it regurgitates into a sensitized esophagus that it causes burning.

Treatment.—In cases of duodenal ulcer of course it is the ulcer that must be treated and not the hypersecretion. Usually antacids are used together with food between meals. Some persons with much gastric stasis get relief from washing out the stomach the last thing at night. Others with a bad ulcer will do well to set an alarm for midnight so as to wake then and take a glass of milk and perhaps some antacid. In some cases a Sippy cure is needed, and in others the patient must be operated on.

Achlorhydria and Achylia

Today most gastroenterologists differentiate the achlorhydria or lack of free acid, which is found in response to an Ewald meal, and the achylia gastrica, in which there is no free acid even after the giving of histamine. In a number of laboratories if there is no free acid in the first sample of juice removed after the Ewald meal, more samples are removed every fifteen minutes for an hour and a half. Sometimes then, after an hour or so a small amount of free acid will appear. If no free acid appears, histamine may be injected to see if this will bring it out.

For years there has been a tendency on the part of some physicians to disregard achlorhydria following the Ewald meal or to minimize its significance. According to them the only achlorhydria with any significance is the one which follows the injection of histamine. To be sure, a lack of response to histamine is important because the person who fails to react to this maximal stimulus can have a primary anemia, while the one, who does secrete free acid, probably has little chance of

ever getting this disease. As was shown by Weinberg (1918), Hurst (19[illegible]), Connor (19[illegible]0) and others, if one examines the stomachs of relatives of persons with primary anemia one can find achlorhydria in two or three times the expected number. Most of these persons, of course, will never suffer from primary anemia, perhaps because they still lack a few bad genes.

The failure of free acid to appear after an Ewald meal probably should not be dismissed so airily as it is now dismissed in many places; it should be given some significance because, if this is the way the stomach responds to meals, there theoretically should not be much chance of the patient's ever getting an ulcer or keeping one active if he has it. We know today that a low pH is necessary if pepsin is to be activated sufficiently to digest protein. Actually, however, it must be admitted that there are a few persons with an ulcer who do not get well in spite of an almost antacid stomach after meals.

In cases of achylia the mucous membrane of the stomach often is markedly atrophic, and the amount of secretion is very small. In other cases, in which there is no free acid, the presence of a considerable amount of combined acid and chlorides will suggest that much acid is being secreted, but it is being neutralized in some way.

In a series of some [illegible],380 apparently normal persons without any lesion demonstrable in the digestive tract Vanzant, Alvarez, Eusterman, Dunn and Berkson[4] (19[illegible]) found that the percentage of achlorhydria met with after an Ewald meal increased steadily with age from about [illegible] per cent at ages from [illegible]0 to [illegible]0 years to about [illegible]0 per cent at the age of 60 years. Similar observations have been reported by other investigators. Many of the persons with achlorhydria have a perfect digestion and never come to any bad end because of the lack of acid.

Years ago Jungerich (1909) and Hoffmann (1918) kept in correspondence with a series of patients with a marked subacidity and found that they did not succumb to carcinoma of the stomach. More recently, however, a number of studies have shown that the patient with achylia, and particularly with the type associated with primary anemia, is more than usually subject to carcinoma of the stomach. This is what one would expect because of the marked atrophy of the gastric mucosa.

Much information in regard to achylia gastrica, the associated atrophy of the gastric mucosa, the lack of the factor of Castle and the anemia which in some animals and man may follow total gastric resection may be found in the chapter on the anemias.

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treatment but in all but a very few cases no such return can be expected It is questionable if the giving of hydrochloric acid helps the situation In cases of gastritis without primary anemia a return of normal acidity can be expected if the lesions should clear up

Value of Gastric Acid in Stimulating Pancreatic Secretion

Since the secretion formed by the action of hydrochloric acid on the mucous membrane of the duodenum is one of the normal stimulants to secretion in the pancreas one would expect that achylia gastrica should produce some failure of pancreatic secretion but according to McClure this is not the case The reason probably is that there are nervous and other humoral mechanisms which cause the pancreas to secrete

Antiseptic Value of Gastric Acidity

Many writers have stressed the importance of the antiseptic value of a strongly acid gastric juice Such an action has been demonstrated and theoretically it should serve to protect the person from many infections of the bowel with harmful bacteria That this action is not of great value to the body is suggested by the fact that so many persons with achlorhydria maintain good health and digestion and never have any diarrhea Henning (1930) made a study of the subject

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In recent years the coming of gastroscopy has thrown light on the ways in which achlorhydria is produced by an atrophic gastritis

Alvarez, Vanzant and Carlson (1936) showed that there is some positive correlation between secondary anemia and subacidity, loss of blood being associated with a lowering of gastric acidity unless a duodenal ulcer is present to maintain the function of the parietal cells at a high level

Diarrhea and Achlorhydria—There is much in the literature on a morning type of diarrhea due to achlorhydria and curable by giving hydrochloric acid It is true that there are such cases but the experience at the Mayo Clinic indicates that they are rare No one knows why this type of diarrhea tends to come at daybreak It has been suspected that the trouble is due to the fact that the achlorhydric stomach tends to empty more rapidly than normal but this should produce diarrhea after each meal

Usually if hydrochloric acid is going to relieve a diarrhea of this type, it does so after the first dose If the acid does not help in a day or two there is rarely much use in continuing with it for weeks or months So far as the writer can remember he has never seen a case in which diarrhea was relieved by the giving of hydrochloric acid when the patient had some free acid in the stomach

Treatment—Many physicians probably give hydrochloric acid in too small a dosage The usual 10 drops is a very small dose It is better to prescribe from ½ to 1 teaspoonful of U S P dilute acid in a glass of water with meals Hurst's dose of 1½ teaspoonfuls would have to be well diluted A little sugar or lemon juice or orange peel may be added to the acid water A drinking tube may be used After taking the acid the teeth should always be rinsed with a solution of sodium bicarbonate As Stafne showed the acid is particularly likely to remove the enamel from the lingual surface of the upper incisors There are drugs which can be given in capsules or tablets to form acid in the stomach, but they form so little that it is hard to see how they can help much

There is no logical diet for the relief of achlorhydria or subacidity If definite gastritis should be demonstrable, this had probably better be treated much as a peptic ulcer is treated with a smooth diet frequent feedings and perhaps antacids It seems logical to remove badly infected tonsils, clean up pyorrhea pockets and discharging sinuses and other sources of pus in the mouth or throat or nose

In cases of primary anemia liver extract will be used There have been a few reports of a return of free acid in the stomach after such

Flatulence

One of the commonest complaints of patients with indigestion is flatulence Always the physician must find out immediately what the patient means by flatulence or gas Is he belching occasionally or repeatedly, or is he bloating or does he feel that gas is trapped in some segment of the gut or is he passing excessive amounts of flatus? Then the physician must remember that the patient may have any or all of these troubles and still have no indigestion The chronic belcher practically always is a neurotic frightened person who is swallowing air and belching it up again

The woman who bloats badly so that she looks pregnant may not be flatulent at all and the roentgenogram made of the distended abdomen will not show any gas in the bowel What she has is some sort of neurosis of the muscle of the abdominal wall A man who feels that he has gas caught in some segment of gut may really have a duodenal ulcer or perhaps some constipation with back pressure toward the stomach and the man who is passing much flatus, may be chewing gum and swallowing much air with the saliva

The Pathologic Physiology of Flatulence

As already pointed out much of the gas that goes down the bowel is not formed through the fermentation of food but consists of nitrogen remaining from swallowed air The carbon dioxide and oxygen are absorbed easily but the nitrogen goes out of the gut very slowly It is as yet impossible to say why some persons swallow so much air Perhaps they have a ropy saliva or they swallow in some peculiar way As Cannon pointed out years ago one can swallow much air in breadstuffs and souffles

In adults the roentgenogram rarely shows any gas in the small bowel If there is any in the bowel it is practically always in the colon Only in infants does one see much gas in the small intestine The concentration of gas in the large bowel may be due partly to the fact that its peristaltic movements are much less active than are those of the small bowel and partly to the fact that its absorptive powers are less than those of the small bowel

It has been shown that carbon dioxide and oxygen can pass quickly through the mucosa of the bowel into the blood and from thence to the lungs Apparently under the influence of emotion or some diseases this

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the abdomen because this may show a segment of small bowel distended with gas (Fig 1) Borborygmus may be the first sign of the development of an obstruction in the bowel due to carcinoma



Fig 1 The roentgenological picture of intestinal obstruction with gas in the small and the large bowel

Especially in older persons the coming of flatulence may be associated with a failing heart or with a type of heart that is overburdened owing to the presence of hypertension In the worst cases there is passive congestion of the bowel and liver Under these circumstances perhaps the gas cannot pass well from the bowel through the liver into the lungs

mechanism for removing gas from the bowel fails to function, and in the worst cases it is reversed so that suddenly large amounts of gas are poured out into the bowel This can be seen commonly during the catheterization of the ureters The first film taken before the urologist gets to work will show no gas in the small bowel while the later ones taken after the catheters are in place may show large amounts of it

As Fine has shown, a man with intestinal obstruction and a badly bloated abdomen can be helped by being given pure oxygen to breathe This produces a steepening of the chemical gradient of nitrogen tension from the gut through the blood to the alveoli of the lungs, and because of this the gas tends more rapidly to leave the bowel

Swallowed air often will pass through the length of the normal bowel easily and rapidly and without cramping whereas gas, which results from the eating of some food to which the patient is allergically sensitive, may appear to remain trapped painfully in some segment of gut for hours at a time Relief may come only when perhaps with the taking of food or the sipping of water waves of peristalsis will again start traveling down the bowel Another maneuver that sometimes starts the gas to moving is walking about This seems to stimulate peristalsis

It is a curious fact that many persons suffer from flatulence only for a day or two before they come down with a cold and then perhaps for several days afterward The virus appears to work some injury to the bowel Most persons with diarrhea also are plagued by flatulence, and this may be particularly true in cases of sprue In these cases the trouble may be due to a defect in the absorptive functions of the mucosa of the bowel In some cases if the diarrhea is stopped rapidly with an opiate, flatulence becomes very distressing

Many persons with their sensitive mucus-forming type of colon suffer much with flatulence especially if they go out to dinner or have guests in the home Young persons have trouble when they go out with a member of the opposite sex Often a vicious circle is started when a little gas forms and cannot for reasons of politeness be passed The distention of the rectum then causes more and more gas to be formed Persons with this handicap often can be helped greatly if they are given a little codeine or paregoric to take before they go out to dinner In some persons flatulence appears to be associated with irritated hemorrhoids or an inflamed and infected anal ring Perhaps this irritation of the rectum causes back pressure in the left side of the colon

Whenever the physician suspects that the patient's discomfort is due to a mild intestinal obstruction, it is well to get a scout roentgenogram of

nervous habit like a tic or the cracking of knuckles which some ignorant persons indulge in when nervous and ill at ease Many persons belch loudly when full of fear that their heart is misbehaving and may stop beating Some of the persons who wake in the middle of the night and start belching loudly may have been wakened by an extrasystole A few may be bothered by the heart strain of hypertension Occasionally the distress is due to the pressure of gas in the splenic flexure of the colon or the patient will be found to have a diaphragmatic hernia In many cases loud belching is due purely to having eaten too much food

In all cases the physician will try to find out why the patient is belching and then will prescribe appropriate treatment Often it helps to tell patients that when they belch repeatedly and voluntarily it is like scratching an itchy place let us say between the toes The more one scratches the more one feels the need for scratching and the only way to get relief is to stop

Bloating

Many women bloat suddenly and rush home to get off a girdle because they have eaten a bit too much often these have cholecystitis Other persons bloat after the eating of some particular food to which they are allergically sensitive Some nervous persons wake in the morning with a flat abdomen and gradually bloat more and more during the day Highly sensitive persons with an overly irritable bowel may bloat suddenly after drinking a glass of cold water or a bottle of pop In these cases it would appear that suddenly large amounts of gas are poured from the blood into the intestinal lumen Curiously some persons will wake up from a nap with a bloated and painful abdomen

Much can be learned about bloating by asking how the swelling goes down Does relief come when gas is passed in large quantities or can relief be obtained by taking an enema? In cases of the nervous type of bloating in which there is no gas in the bowel the patient will say that she never has any flatus and the swelling goes down without the passage of gas Usually it goes down during the night This is a nervous disease related to hysteria In some cases bloating is due to constipation and can be avoided if the patient will take each morning an enema consisting of perhaps 1½ quarts of warm physiological salt solution In other cases it can be cured by finding the foods that cause trouble allergically Milk and eggs are common offenders

Much can be learned sometimes by asking the patient if the flatus has a foul odor Odorless flatus is likely to consist mainly of swallowed

In some persons it is possible that flatulence may be due to the presence of a heavy infestation of the bowel with some intestinal parasite. Especially when the person has been on a trip to some warm country, it is well to have the stools examined.

Another common cause of flatulence is the abuse of laxatives and purgatives. No physician should start the treatment of flatulence without knowing what drugs the patient is taking. In some cases he or she may be taking too much of some gummy laxative or hydrocarbon oil. Occasionally nowadays flatulence and cramps are due to the taking of large amounts of concentrated vitamins.

Belching

An ordinary single "burp" probably is due to a reverse wave coming up to the esophagus from an overly full stomach, but repeated belching, as has been stated already, is due practically always to the swallowing of air. This air goes down as far as the cardia and then is returned. Roentgenological studies show that only occasionally can some of this air be forced into the stomach. Only once in years will the roentgenologist see a person with a gas bubble at the top of the stomach so large that he or she could get many belches out of it.

When a man belches repeatedly because of air-swallowing, it is usually because he is nervous and frightened and trying to relieve a feeling of distress around the cardia. He will go on belching for many minutes, perhaps, hoping that eventually he will get up one huge belch which will give him relief. Sometimes this does happen. Perhaps after taking a little solution of bicarbonate of soda there will be a big belch and the regurgitation of a mouthful of gastric contents, and with this there will come relief. Apparently with the running out to the pharynx of one big reverse wave, some ectopic center in the stomach or duodenum that was sending the waves orad quiets down, and then the man feels relieved, just as he would be if an attack of auricular fibrillation were suddenly to stop. Similarly a man who is terribly nauseated can get instant relief from one big belch or from the regurgitation of a mouthful of food.

It is not sufficient to tell the patient that he is swallowing air and must stop it. Sometimes an intelligent and strong willed patient, when he is convinced that he is swallowing air and in a way scratching himself with it, will immediately stop the process. Often it would seem to be a

In some cases the relief of flatulence can be obtained only by operating on a diseased gallbladder or an ulcerated duodenum In most cases in which there is marked bloating without any gas in the bowel the treatment must be along psychotherapeutic lines The patients are practically all women and usually women who have had an unhappy marriage or love affair *There is good reason to believe that the mechanism producing the bloating is a spasm of the muscles surrounding the abdominal cavity a spasm which in some way pushes the abdominal contents forward* Often in these patients the abdomen will go almost flat if the patient is put on her back with knees up In other cases an injection of morphine will put a stop promptly to the bloating I have seen it disappear instantly when the patient vomited, or when she was given a spinal anesthetic In one case the patient, who previously had been terribly crippled by this illness, got well when her dipsomaniac husband died

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air, whereas foul flatus is likely to be due to indigestion and particularly to the eating of some food to which the patient is allergically sensitive. Occasionally foul flatus is due to the coming of diarrhea. With this there is probably some churning of the air in the colon with the foul fecal material. In many cases foul flatus is due to the patient's eating so much that he overwhelms the digestive powers of his digestive tract.

It is a curious fact that when increased flatus is due to constipation gas may keep pouring out so long as there is a plug of feces in the rectum. The minute this is removed the formation of gas stops.

In trying to find the cause of flatulence it helps to have the patient take an enema every day for a while so as to see how much good comes from keeping the colon clean. In many cases also the patient should remain for a few days on an elimination type of diet such as is used in the study of patients possibly allergic to some food.

It may be helpful diagnostically also to put the patient for a time on a smooth type of diet without much roughage. In many cases this so improves digestion that there is less formation of gas.

While questioning 500 patients as to the foods that they knew would give them gaseous distress, Hinshaw and I found that most persons complained first of onions. Next in order of frequency the foods most commonly blamed were cooked cabbage, raw apples, radishes, dried beans, cucumbers, milk, fatty or rich foods, melons, cauliflower, chocolate, coffee, lettuce, peanuts, eggs, oranges, tomatoes and strawberries.

The Treatment of Flatulence, Belching and Bloating

As has been pointed out, the successful and logical treatment of flatulence, belching and bloating depends on the making of a good diagnosis as to the type of trouble that the patient has. Naturally it is useless to give a smooth diet to a patient who is belching loudly simply because he is scared to death about heart disease.

I have not had much success with the use of carminatives. An alcoholic drink sometimes works fairly well and peppermint may be helpful. In bad cases a teaspoonful of camphorated tincture of opium may work well. Sometimes the taking of a little food or walking around will start the gas to moving and will bring relief. A number of the carminative tablets on the market contain charcoal, but it is very doubtful if this substance can have any value when wet; it does not absorb gas. The sipping of water often is helpful because it tends to start waves running down the bowel, waves which will move the gas out of segments of gut in which it appears to have become trapped.

out of his nose In 18 cases marked regurgitation did not cause burning In some the material regurgitated was bile stained and evidently had come from the duodenum or jejunum Apparently the mucosa of the esophagus must be sensitized first if the patient is to feel burning This was suggested by the fact that in some cases the material regurgitated burned the nose but not the esophagus Twenty of the patients belched often while 21 did not Some noticed stabs of burning when they belched

Immediate Causes of Heartburn

The 123 patients mentioned a number of things which caused them to get heartburn Common causes were eating too fast or too much Eighteen persons knew that if they ate too much they would get into trouble Most of the sufferers knew that the eating of certain foods would bring the burning The commonest foods mentioned were fats coffee onions seasonings radishes tomatoes oranges eggs cucumbers chocolate pepper cabbage fried foods meats gravy apples milk and sweets

Some persons got heartburn if they took too much liquid with a meal This seemed to favor regurgitation Some of the persons were allergic to certain foods Others got heartburn within fifteen minutes after taking acetylsalicylic acid (aspirin) or some other drug Quite a few got into trouble from drinking alcoholic drinks Some had trouble with certain types of alcoholic liquor but not with others Fifteen sufferers said that tobacco was one of their worst enemies One said that smoking a cigar would make him suffer for days afterward Curiously in his case the smoking of a package of cigarettes gave no trouble

Thirty two of the patients had noticed that outbursts of anger were bad for them Curiously a violent argument might bring the heartburn on the following day Apparently it took some time for sensitization of the esophagus A few persons were made worse by constipation which increased a tendency to regurgitate Some were made worse by lying down or bending over shortly after eating This favored the regurgitation of gastric juice In some cases heartburn followed violent exercise such as playing tennis Only one patient in 4 of those examined had actual hyperacidity of the gastric juice Some had little acid, and a few had none

Treatment

Persons with heartburn get most relief from taking a solution of sodium bicarbonate in water As one would expect the taking of alkaline

Heartburn

By heartburn is meant usually a sensation of severe burning under the sternum. Sometimes with this there is an element of pain or a feeling of spasm. Occasionally there is a feeling as if waves were coming up the esophagus. When asked to show where the distress is felt, the patient points to the lower end of the sternum and then runs the hand upward a variable distance toward the neck or pharynx.

Heartburn tends to come in spells which may last from days to weeks, months or years. These spells often come and go suddenly without any cause that the victim can discern. Apparently what happens is at the beginning of a spell is that the gastric juice begins to regurgitate into the esophagus where it soon makes the mucosa so hypersensitive that there is distress for days or weeks afterward. In some cases it may produce esophagitis. Once this comes, the patient has to be in misery for several days. It is curious that attacks of heartburn will come sometimes after one meal such as supper and not after another meal such as breakfast. Occasionally patients are waked at night by the distress and have to sit up. If with some indiscretion of eating, drinking or smoking a man starts an attack of heartburn, he may be in trouble for two or three days.

A study of 123 cases made by the writer indicated that heartburn is not due to any of the known organic diseases. It is associated sometimes with ulcer, but curiously, when the patient is having ulcer pain, he has no heartburn and vice versa. In 5 of the 123 cases the patient had a small diaphragmatic hernia which may have been contributing to the trouble. Curiously, 3 patients had carcinoma of the stomach with low acidity of the gastric juice. Usually a person can have heartburn off and on all his days without coming to any bad end because of it. The disturbance appears to be more commonly met with in Jewish men. It tends to run in families. It is commoner in men than in women.

Of the 123 patients studied there were 29 who were troubled with regurgitation and 34 who did not have it. Twenty were much bothered by it. Evidently then reverse peristalsis which causes gastric material to run back into the esophagus is commonly associated with heartburn and it seems probable that it is the principal cause of the distress. However some of the persons questioned felt that there was no association between their regurgitation and the heartburn. Certain it is that many persons regurgitate often without ever getting heartburn. One man in the group studied often waked at daybreak with acid fluid running

rare cases it is found in a person who has cholecystitis or an ulcer treatment of the organic disease is not likely to influence the regurgitation Occasionally one can see a woman with this trouble who has been operated on five or six times without benefit Sometimes the condition is associated with anorexia nervosa and sometimes the patient is definitely psychopathic In some cases the regurgitation comes when the patient is tired or nervous or is under great strain and it goes away when she is rested Some of these persons can regurgitate for years without losing weight while others become very thin Sometimes as is often the case with hysterical women the patient is not concerned over the situation and it is the relatives who bring her in

Treatment

Treatment should consist of acquainting the patient with the nature of the trouble and assuring her that it is functional and to some extent a bad habit It is a habit that can grow on her and can wreck her life as a social being Often the patient will say that she could stop it easily enough if it were not for the pain in the epigastrium which comes when she holds the food down That a quick cure is possible through will power alone was shown by one woman who began to regurgitate badly when her husband was called for the draft When she was told that her trouble was functional and due to worry she said Then I will stop it I must because when my husband goes to war I will have to run the business That day she stopped regurgitating

For many persons it probably is a difficult and painful process to hold the food down Sometimes the food will come up in spite of them as is shown by the fact that they will regurgitate when dining out Sometimes the cure can be worked only by putting the patient in a hospital and in the worst cases in which the patient has a revulsion for food and regurgitates it as fast as she swallows it she may have to be fed through a tube for a time It may help at first to supply plenty of protein in the form of a digest of amino acids There now are several such preparations on the market

After these persons are cured some learn that the return of regurgitation always means that they are getting tired and in need of a rest

Anorexia Nervosa

Anorexia nervosa is a condition in which the patient usually a young woman refuses to eat and as a result goes down to skin and bones

tablets does not work so well Occasionally relief is secured the minute a big 'burp' comes up With this reverse peristalsis quiets down Some patients get relief by the taking of food The taking of milk does not give such good relief as is obtained by patients with ulcer Sometimes it makes the patient worse Some persons can "put out the fire" by drinking water while others get more distress Sometimes a laxative will give relief for several days perhaps by stopping the tendency to reverse peristalsis in the digestive tract

Regurgitation or So-called Nervous Vomiting

There is a syndrome commonly observed in nervous young women in which the patient begins to regurgitate food soon after leaving the table or perhaps even before The girl may have to jump up in the middle of the meal and hurry to the bathroom It is unfortunate that this disease usually is described under the heading of "nervous vomiting", because the essential point in the diagnosis is that usually it is not vomiting that these people complain of but regurgitation, as in the case of a baby the food keeps coming back in mouthfulls without the accompaniment of either nausea or retching The stomach does not struggle with the food for several hours and then force it all up at one time That is the sort of true vomiting that occurs with a pyloric obstruction

Sometimes a regurgitator will keep bringing up food into a handkerchief as she sits in the physician's office Many a patient will explain that she regurgitates in order to get relief from a distress or pain that comes in the epigastrium soon after she eats If she tries to hold the food down, the pain gets worse and worse

In nearly all cases the woman is nervous perhaps constitutionally inadequate or somewhat psychopathic Often she is unhappy and often she is caught in some kind of a trap The first question the physician should ask these women is 'are you caught in some unhappy situation from which you can see no way of escape ' In many cases for one reason or another the girl is held at home perhaps by a sick or dominating mother, and is not able either to marry or to go out into the world to work and lead her own life

Occasionally there appears to be a family predisposition to regurgitation and one can get the story that some of the relatives ruminate that is when they regurgitate they chew the food and swallow it again This disease seldom appears in men and when it does the man sometimes is not very masculine

The trouble probably is always a functional one and even when in

Treatment

Naturally treatment must consist largely of psychotherapy and partly of efforts to get the patient to eat more and then hold it down If the patient cannot get a good insight into her condition if she cannot see that the home situation brought it on if she is too psychopathic or too unintelligent to help herself or if the home situation cannot be improved the prognosis is bad Sometimes for a while if relatives will come to the rescue and pay for a course of treatment in a hospital the patient will gain weight but as soon as she goes back to the old life she is apt to break down again

Indigestion and Abdominal Discomfort Due to Cerebral Arteriosclerosis With Minor Apoplexies

The gastroenterologist sees many patients usually past forty with a vague indigestion and a vague abdominal distress They often have a nervous breakdown and many have lost much weight Usually careful questioning will reveal the fact that the patient s worst trouble is a sense of misery and fatigue and loss of energy The old joy in life is gone There may be some nausea and perhaps, pain immediately after eating Very helpful diagnostically when it can be elicited is the story that the trouble all started suddenly one day with perhaps a collapse a fainting spell or an attack of dizziness

At first sight it may appear that the patient must have a carcinoma beginning somewhere but the most careful roentgenological study of the digestive tract and the rest of the body will fail to show any sign of tumor formation Furthermore the hemoglobin reading may be high and the blood sedimentation rate low Perhaps also it will be found that the patient has been living for years in a state of misery without losing any more weight or without coming to any bad end

Some of these persons will be found to have hypertension with arteriosclerosis and roentgenograms of the base of the skull may show calcified internal carotid arteries The patient may appear older than his or her age and often work has had to be given up The most significant point often is that in a moment or a day or two a person who had been energetic happy and well became incapacitated and utterly miserable ill and discouraged apathetic depressed and unable to work

Oftentimes in these cases if the physician will suspect what has

These patients are practically all of the same type, more or less psychopathic, shy, mentally inaccessible, sex hating, constitutionally inadequate and dependent on others. Recent studies have shown that most of them come from homes in which they were unhappy and dominated and ordered about by a mannish, sex hating mother who had little use for the weak, inefficient and perhaps alcoholic father. Often one finds the patient caught in a trap, since the mother always scares away the occasional man who shows any interest in the girl. If the girl has gotten a husband one finds usually that the marriage has been unsatisfactory, and sex relations have been abhorrent. Often psychiatric investigation shows that the girl, who appears to love the mother, is really harboring much resentment against her. Sometimes the intelligence quotient is not high, and the patient either refuses to gain insight or is unable to do so or to co-operate with the psychotherapist. Occasionally the situation may represent a flight into illness. Often, as in cases of hysteria, the patient is not much concerned over her situation and not much interested in trying to get well. It is the family who become concerned.

Berkman, who studied many of these patients, found that some of them had had an attack of encephalitis before their anorexia appeared. Probably some regulatory center in the hypothalamus was injured. One man with what looked like this disease was found at necropsy to have a large cyst in the cerebellum, and another man had a tuberculous abscess in the psoas muscle. Evidently the picture of marked anorexia with emaciation can be produced in different ways in different persons.

For a while some physicians thought that many cases of extreme anorexia were due to Simmonds' disease, but today this disease is thought to be very rare. As Berkman (1930) pointed out, in almost all cases of anorexia the sella turcica is normal in shape and size. Occasionally severe anorexia may be due to melancholia or a form of insanity in which the patient fears that the food is poisoned or has been denied to her by God.

Naturally, after one of these patients becomes very thin, the blood pressure is low, the pulse rate slow, the gastric acidity low, and the basal metabolic rate decidedly low. This is not due to any disease of the thyroid gland, and the giving of desiccated thyroid usually does not help. Menstruation usually ceases, probably because of the malnutrition. Curiously these persons usually do not become very anemic, and they rarely show any nutritional edema or any sign of lack of vitamins.

Incidence

In Nuzum's 1,000 cases of tabes dorsalis gastric crises were the initial symptom in 17 per cent. Simons concluded from the experience of several writers that probably 12 per cent of tabetic patients have gastric crises.

Etiology

Aside from the fact that the cause is syphilis of the nervous system almost nothing is known about the mechanism through which the crises are produced. According to Bennet and others it is noteworthy that most crises occur in the preataxic stage of tabes. Simons was unable to find any record of necropsy studies made to compare the details of destruction of the nervous system in tabetic patients with crises with the details of destruction in tabetic patients without crises.

Symptoms

As already noted, crises often tend to begin suddenly and to end suddenly. They may last for from a few hours to a week or more. The severity varies markedly, but often the pain is agonizing. Retching also may be extremely fatiguing. The pain is often so bad that even large doses of morphine will not control it. The pain may spread up and down the body. It may seem both superficial and deep. There may be a sensation of a painful lump somewhere in the upper part of the abdomen. Because of the constant vomiting the patient may lose much acid and get into a state of alkalosis. Great quantities also of chlorides and water are lost. The free interval between attacks may be as long as several months.

Striking and highly diagnostic when present are areas of hyperesthesia of the skin of the abdomen or lower part of the thorax. Roentgenoscopical examinations made during crises have shown marked spasm of the stomach and bowel. A surgeon who because of a mistaken diagnosis operated on a patient during a crisis told Simons that he found the small bowel contracted down to the diameter of a pencil. Occasionally there is some diarrhea during a spell.

Physical Findings

It is helpful diagnostically to note that usually there is no rigidity of the abdominal wall and rarely any deep tenderness in the abdomen.

happened and will question the patient and his family carefully enough, he will get a story of one or more episodes which strongly suggest minor apoplexies Perhaps there was a fainting spell, or the man became very dizzy, or for a moment he fell out of his chair, or he woke with a miserable head on him and after that his memory was bad, his hand writing was changed and he was irritable or weepy or much changed in character and temperament Usually the diagnosis at the time was a 'heart attack , but the facts that the man's wind still is good, that he still is able to walk without getting anginal pain and that his electro cardiogram shows no definite signs of coronary thrombosis all make it appear unlikely that the heart was affected It is far more likely that what took place was thrombosis of a small artery in the brain

In many cases even when the physician considers the diagnosis of cerebral arteriosclerosis with a small apoplexy occurring perhaps during the night in the absence of muscle weaknesses and abnormal reflexes he may not feel justified in making the diagnosis Only later, as months or years pass and the patient fails to improve or gets new and more typical little apoplexies will the physician be sure of what has happened and is happening to the man s brain

The symptoms in the abdomen can be produced perhaps in two main ways The generalized distress in the abdomen is probably a paresthesia, referred out from the diseased spot in the brain to the periphery It often comes like a flash at the time of the little stroke In other cases with the little stroke some sort of a storm appears to go down the vagus nerves to produce a spasticity of the muscle coat lining the gastrointestinal tract As soon as the patient eats there is spasm and pain Usually this clears up after some months

Treatment

Naturally there is not much real treatment available for this disease This topic has been discussed in more detail in the chapter on cerebral arteriosclerosis with small apoplexies in Vol VI Chapter II-A

Gastric Crises of Tabes Dorsalis

Definition —Gastric crises are paroxysmal attacks of abdominal pain often with vomiting which occur in a person suffering from tabes dorsalis The duration of a spell may be from hours to weeks

mann test will give negative results, but the very sensitive Kline test and the Hinton test may show some abnormality

The physician of course should always be suspicious when there is marked hyperesthesia of the skin over the abdomen A leukocyte count should be made A slight rise should be discounted because this can be due purely to pain A scout or preliminary survey roentgenogram of the abdomen can be made to rule out pneumoperitoneum such as would follow the rupture of an ulcer It could also show stones somewhere or it could show the typical picture of obstruction of a segment of bowel The urine shuld be examined immediately to see if there are any red blood cells which would indicate the passage of a stone down the ureter

Occasionally one can get a history of rectal or vaginal crises sphincteric disturbances impotence increasing deafness or queer feelings in the legs and feet It should be remembered that a certain number of patients with tabes also have duodenal ulcer If the roentgenological study does show an ulcer it should be remembered that rarely does an ulcer produce such violent symptoms It can do so however if it perforates posteriorly into the head of the pancreas

The blood amylase can be studied to see if there is any sign of acute pancreatitis Because the pancreas is behind the peritoneum and the posterior perforation of an ulcer is also behind the peritoneum in these cases there will be no abdominal rigidity In a woman of course the pelvis will have to be examined carefully to rule out acute salpingitis

Prognosis

According to Simons gastric crises can disappear in 44 per cent of cases following routine treatment for syphilis and can become less severe in 5 per cent In some cases the crises for a time will get worse and worse while in many they tend to fade out with time The patient may then have a bit of pain for a time after defecation in the morning and then he will be free for the rest of the day

Treatment

There is no good treatment for gastric crises In the worst cases nothing but morphine dilaudid or demerol in large doses will do any good and even these drugs will not always give complete relief Many

Some have claimed that the blood pressure is elevated in cases of vomiting due to gastric crises while it is lowered in other types of vomiting.

Unfortunately for the diagnostician the common signs of tabes are often absent in these cases. Oppenheim (1911) stated that the pains may come from 10 to 20 years before the other symptoms of the disease appear. In one series of cases the knee jerks were present in more than 25 per cent of these early tabetic patients. Stokes (1935) found that 40 per cent of 3[illegible] patients with neurological evidences of tabes dorsalis but with a negative spinal fluid and negative Wassermann reaction had gastric crises. Simons said that some 20 to 25 per cent of tabetic patients, who have crises, must be expected to have a normal cerebrospinal fluid or a fluid which shows only minor abnormalities.

Diagnosis

Partly because tabetic crises are rare, and the physician often fails to think of them, and partly because they often occur in persons who have practically no signs of tabes, many of the patients get operated on. According to Nuzum (1916) a group of 87 of these patients had had a total of 97 futile operations. One was operated on five times before someone diagnosed tabes. That the average physician is not always to blame for such a mistake in diagnosis was shown by the fact that the writer had one of these patients referred to him by a nationally eminent neurologist, who said that the man could not have tabes and, therefore must have either gallstone colic or a perforated ulcer. Fortunately before the patient's abdomen could be explored, it was noted (1) that one pupil was somewhat irregular (2) that he had a marked area of hyperesthesia over the region of the liver and (3) that he was having trouble with urination. The minute the urologist examined him he diagnosed a cord bladder, and studies of the cerebrospinal fluid then showed changes typical of tabes. As commonly happens the man's knee jerks were good and he did not sway when standing with eyes closed.

The experienced clinician probably should suspect always a tabetic crisis whenever he sees a patient with attacks of severe pain or retching without any rigidity of the abdominal wall or any deep tenderness. The diagnosis will be fairly easy, if a history can be *obtained of* several previous attacks which came suddenly out of a clear sky without relation to eating. One may be able also to get a history of syphilis *in the past* probably without adequate treatment. Perhaps the conservative Wasser-

Gastroptosis

Definition

By ptosis generally is meant the downward displacement of an abdominal organ when the patient is in the standing position Usually the viscus returns more or less to its textbook position when the patient lies down

There are two objections to the term gastroptosis One is that strictly speaking there is no such entity because ptosis' of the stomach generally is associated with an unusual mobility of other organs such as the colon kidneys liver spleen and uterus and the other is that a true dropped stomach has never been seen The cardia is fixed at the diaphragm in such a way that it cannot descend and hence what are called dropped stomachs are really only elongated stomachs Although this may seem to some to be a distinction without a difference its earlier recognition probably would have saved much excitement and perhaps the wastage of several barrels of printer s ink

Although Glenard wrote about enteroptosis in the 80 s it was not until about 1910 when the roentgen rays began to be used extensively in the diagnosis of gastrointestinal diseases that physicians became alarmed about the many stomachs which they found reaching down into the pelvis Unfortunately it did not occur to them that never before had they seen this organ in a normal living unanaesthetized person in the standing position Since at operations and necropsies the stomach always looks like the one originally depicted in Gray s Anatomy it is not surprising that physicians became excited when they discovered the long stocking like tube which shows up so often on the fluorescent screen They felt that such a stomach must be distinctly pathological and symptom producing and they immediately set about devising ways and means of putting it back under the ribs where they thought it belonged Soon however those physicians who had occasion to screen large numbers of men and women began to get over their alarm, they found the long type of stomach so frequently that they became accustomed to it and finally in many offices they ceased to pay any further attention to it

Moreover many observers soon noticed that there is often a relation between body build and the position of the stomach Short stout thick-necked and well muscled persons often have a stomach of steer horn type extending from left to right across the abdomen and close to the

writers have recommended all sorts of drugs, but the experienced clinician will have so little faith in them that he will hardly want to try them Thus some men have advised giving from 1 to 3 mgm of atropine sulfate intravenously and others have given 0 6 c c of epinephrine subcutaneously Others have given per rectum 40 grains (2 6 gm) each of chloral hydrate and sodium bromide in water The intravenous injection of 0 3 gm of phenobarbital sodium might help by cutting down the irritability of the vomiting center Simons said that Stokes has found that bending the patient backward over the foot of the bed until his feet fly out from under him will sometimes cut short an attack

As one would expect the routine treatment for syphilis cannot be expected to work a cure because damage to the nervous system already has been done somewhere but according to the Co-operative Clinical Group in 118 cases of gastric crises 44 per cent were relieved by such treatment In other cases one can try Swift-Ellis treatments Some writers advise the use of the Kettering apparatus for the production of fever but Simons said that the induction of fever sometimes will bring on a violent attack He prefers the malaria treatment

Naturally during a prolonged attack it is well to combat dehydration and starvation by injecting into the veins fluids salts glucose and perhaps, amino acids

Many surgeons have tried to cure crises by operations on the posterior nerve roots the vagi or the spinal cord but usually with poor results Since the disease probably is in the spinal cord and in the brain one can see easily why cutting nerves or nerve roots can fail If posterior nerve roots are to be severed many must be cut and the operation must be extended high up in the thoracic region The sympathetic chains must be cut also because sensory fibers travel through them to enter the cord high up

If cordotomy is to do any good the cuts must be made high up above the place where sensory fibers from the gastric region come in Unfortunately this operation often fails to relieve the pain and it may easily leave the patient with a bladder which does not empty properly

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professional athletes dancers and prize fighters From that time on he lost interest in prescribing abdominal exercises for his patients

Those writers who believe that the weight of the feces drags down the bowel and produces serious kinks and membranes should look some day into a toilet bowl and note that feces ordinarily float Modern plumbing actually is developed about this fact Next they should take the entrails of a rabbit and throw them into water to note again that they float Then they should read the reports of those men who have studied the dynamics of the abdominal cavity and have found that the various organs with their specific gravity so nearly that of water practically float one on the other For this reason a cecum in situ may weigh less when full of feces than when empty just as a bag full of cork will weigh less in a bucket of water than in the air

The occasional surgeon who still feels inclined at times to fasten up a kidney, a stomach or a colon should remember that its attachments or so called *ligaments serve only as guy ropes, they do not hold the viscus up It really floats on the other abdominal organs* and it would sink the minute the pelvic floor or the abdominal wall were to give way The liver will fall away from the diaphragm most startlingly if with the subject in the erect position some gas is injected into the peritoneal cavity This shows clearly that conditions in the abdomen are much like those in a well corked hot water bottle which has a little water but no air in it Hang such a bottle by its neck and the water will remain in contact with the plug, let in some air, and let the water drop immediately to the bottom

Actually the stomach and intestine are tubes in which material is moved onward by muscular force The exact orientation of the different parts of this tube in the abdomen need hardly concern anyone so long as the muscle works properly The force of gravity has been shown to have a little effect on the emptying time of the stomach and on the rate of travel of heavy *indigestible substances through the bowel but for the most part it would seem to be a negligible factor in the mechanics of the digestive tract*

Bedingfield gathered together most of the literature on ptosis Barclay made a valuable study of the degree of mobility of the stomach and colon as his subjects stood up lay down or rolled from side to side

Symptoms

It not infrequently happens of course that persons with long stomachs have indigestion In many cases it must be a coincidence and in

under-surface of the liver while tall, thin, long chested men and women with a narrow abdomen commonly have a long, low-lying stomach

Stiller wrote a book on the asthenic constitution and emphasized the diagnostic importance of a narrow intercostal angle and a floating tip to the tenth rib Bryant wrote on "herbivorous and carnivorous types of man and Mills described sthenic and hyposthenic types

Although most of the leaders in the profession have lost their interest in enteropotosis as a pathological condition, there are physicians who still continue to diagnose and treat it as a disease and this in spite of the extensive work of Moody Van Nuys and Chamberlain, who showed after examining hundreds of college athletes that ptosis is more normal than abnormal

Moody roentgenographed the stomachs and colons of over 1,000 healthy university students in California and England and showed that the lowest portion of the greater curvature of the stomach was below the interiliac line a line drawn between the highest points on the iliac crests in 74 per cent of the men and in 87 per cent of the women In 25 per cent of the men and in 46 per cent of the women it was more than 5cm below this line and in 7 6 per cent of the women it was more than 10 cm below The greater curvature of the normal stomach may be found at any point between 7 3 cm above and 13 7 cm below the interiliac line Even the lesser curvature in the antral region was found below the interiliac line in 13 1 per cent of the men and in 28 8 per cent of the women, and in some cases the pylorus was below the line

It will be seen then that the lower end of the stomach can be found in the true pelvis of men and women who are perfectly well Furthermore Moody found no constant relation between the position and shape of the stomach and the strength and build of the individual The most powerfully muscled man and the most powerfully muscled woman among his subjects each had 'gastroptosis", with the pars pylorica well below the interiliac line In the group of students studied it was found also that the transverse colon so commonly is situated in the pelvis that this must be looked upon as its normal position

Another observation of Moody's which will be disappointing to ardent therapists, is that the development of the abdominal muscles has little to do with the position of the stomach One man trained himself until he could sit up from the reclining position 300 times without resting but his greater curvature failed to move upward The writer discovered this fact in 1913 when he found gastroptosis' in a number of

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others the symptoms are due really to the same fatigue, overwork, insomnia or undernutrition which resulted in loss of body weight and muscular tone and in a lengthening of the stomach It it possible, too that in some cases the loss of tone of the stomach and perhaps its low position do contribute somewhat to the causation of symptoms So far as is known, there are no symptoms due to a lengthening of the stomach per se The presence of a long stomach will be suspected always in tall, thin persons, it can be detected often by the low position of the splash sounds when the stomach is thrown back and forth between the palpating hands, and it can always be determined with the help of the roentgen rays and the barium meal

It must never be forgotten also that the discovery of a marked degree of enteroptosis does not relieve the physician from the responsibility of looking for cholecystitis ulcer carcinoma pulmonary tuberculosis pelvic disease or the many other conditions which may cause indigestion

Treatment

There is no doubt that many enteroptotics feel better for rest, overfeeding and proper corseting This does not mean however, that they feel better because the lower border of the stomach has been raised a few centimeters Generally a certain amount of rest has to go with overfeeding if the patient is to gain weight and much of the benefit derived must be ascribed to this With better nutrition there often goes a better appetite calmer nerves and a greater sense of well being The increased comfort which many women derive from corseting seems often to be due to the better support to the spine and perhaps also to the increase in abdominal pressure The rest cure and the use of the overfeeding diet have been described under functional disorders.

The best type of girdle for women with a flabby abdominal wall is probably a good commercial one such as can be bought from any corsetiere The heavy corsets with belts and pads are hardly necessary

If the patient is put to bed for a while the foot of the bed should not be raised This can only cause discomfort

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difficult menstruation will get an acute digestive upset with nausea and vomiting a day or two before the period With this there will often be diarrhea

There is some evidence to show that there are substances of bacterial origin which, before or after the death of an animal can pass through the wall of the bowel and into the muscles which later are to be used for meat It has been found that an extract of such muscles when injected into mice will produce violent enteritis and death It is possible therefore that some of the upsets that follow particularly the eating of chicken, turkey or game are due to the passage of such toxins into the meat

Acute Gastritis With Intestinal Upsets

Physicians often assume that the cause of a sharp attack of indigestion is an acute gastritis and it is probable that at times this is true Nowadays the diagnosis could be confirmed easily with the help of a gastroscope but usually in the acute stages of the disease this instrument should not be passed Always it must be remembered that there is a bowel as well as a stomach and that the indigestion can be due to enteritis as well as to gastritis Perhaps in many cases the mucosa in the stomach and bowel are involved together

In these days when so much interest is being displayed in the subject of gastritis it is well to remember the description by Beaumont of the changes which appeared occasionally in the gastric mucous membrane of Alexis St Martin In his Experiments and Observations on Gastric Juice' (1833) page 107 Beaumont wrote

In ferbile diathesis undue excitement by stimulating liquors overloading the stomach with food fear anger or whatever depresses or disturbs the nervous system the villous coat becomes red and dry at other times pale and moist and loses its smooth and healthy appearance the secretion becomes vitiated greatly diminished or entirely sup pressed, the mucous coat scarcely perceptible the follicles flat and flaccid

There are sometimes found on the internal coat of the stomach eruptions or deep red pimples, not numerous At other times irregu lar circumscribed red patches are found There are also seen at times small aphthous crusts in connection with these red patches Abrasions like the rolling up of the mucous coat into small shreds are not an uncommon appearance

Acute Gastritis or Transient Indigestion

Obviously an attack of acute or transient indigestion can be due to many causes and often the patient will have recovered before the physician can guess what the trouble was A common cause may well be the eating of too much food when the person is nervous and tense and upset about something In innumerable cases some food is blamed for the upset, and the first impression is that it was spoiled in some way and irritant to the digestive tract but this may seem doubtful, when it is found that other persons who partook of it were not upset In some cases the indigestion may be due simply to eating too much or to eating too much fat In other cases the indigestion may be due to eating some food to which the person is sensitive In bad cases the trouble is due to the eating of food which has been contaminated with bacteria, perhaps of the salmonella or enteritidis group paracolon and paratyphoid being names formerly in use In many cases the creams which go into pastries such as cream puffs and chocolate eclairs, become heavily infected with the bacteria of mouse typhoid or with staphylococci

In the cases in which the food becomes heavily infected with some organism the patient is likely to be severely ill with fever, abdominal pain diarrhea and perhaps vomiting These are the cases which in the old days were diagnosed as due to ptomaine poisoning Today chemists do not use the word ptomaine

In some cases an acute attack of indigestion will prove later to have been due to an attack of appendicitis or cholecystitis or a flare up in an old ulcer In recent years some acute attacks with vomiting and diarrhea appear to have been due to a virus which has spread through the country in epidemic form In these cases the abdomen usually is not sore, there is little if any pain or fever and the patient recovers quickly

In older persons the diagnosis of acute indigestion generally means a small stroke of some kind and often a thrombosis of some small intracranial blood vessel In other cases when nausea and vomiting are associated with vertigo ear noises and perhaps some deafness the cause is Meniere s disease Especially in children an attack of indigestion may be ushering in some acute infection In older persons it may usher in a cold

Often the physician must think to ask if the patient is migrainous, because in that case an attack of nausea and vomiting may represent an attack of migraine with only a mild headache perhaps so mild that the patient does not think to mention it Some nervous women with

that errors in diet are the chief cause Especially important he thought is the mechanical irritation caused by the presence in the stomach of large amounts of imperfectly chewed food Other causes might be irritation by cold drinks alcohol spices and spoiled food He thought that gastritis is associated frequently with enteritis Schindler once gastroscoped a patient on the second day of an acute digestive upset and found the mucous membrane covered with thick mucus Henning in cases of acute gastritis also found thick mucus with reddening of the mucosa and occasional hemorrhages According to Schindler the disease lasts from one to eight days but the patient may feel weak and uncomfortable for some time after that Usually the condition in the gastric mucosa clears up entirely (Schindler 1937, p 174)

Treatment —Schindler suggested that vomiting be induced by the drinking of warm water Emetics should not be used The giving of a laxative may help but it can also delay recovery The warmth of an electric pad over the abdomen may be agreeable No food should be taken the first day and very little for a few days after that Water may be taken from the start In order to keep the patient from going into a chronic state of indigestion it is well to have him eat but little for several days after the trouble seems to have cleared up

Infectious or Toxic Acute Gastritis

According to Knud Faber there is a form of acute gastritis which is produced by the toxins of bacteria or viruses entering the stomach from the blood stream This hematogenous form of gastritis is supposed to go with infectious diseases such as measles scarlet fever, diphtheria influenza pneumonia variola typhoid and yellow fever

Schindler (1937) has stated that in this disease the gastritis spreads over the entire stomach Erosions are common and often there is a hemorrhagic inflammation with leukocytic infiltration

There is likely to be loss of appetite perhaps vomiting but rarely vomiting of blood The prognosis generally is good Treatment consists of a light diet until the patient feels better

Epidemic Transient Vomiting and Diarrhea of Unknown Origin

In recent years in many parts of the world there have been epidemics of violent vomiting and diarrhea in which the symptoms usually last for

'These diseased appearances, when very slight, do not always affect essentially the gastric apparatus When considerable, and particularly when there are corresponding symptoms of disease, as dryness of the mouth thirst, accelerated pulse etc no gastric juice can be extracted Food taken in this condition of the stomach remains undigested for twenty-four or forty-eight hours

It is interesting to note that apparently these changes were not due to inflammation but perhaps to some change in the circulation of the mucosa Often when these changes were present St Martin did not seem to notice them Sometimes the changes seemed to be due to constipation because after the taking of a purge the mucous membrane rapidly regained its normal appearance

Similar observations were made by Carlson in the case of his gastrostomized man, whom he studied for years During colds or attacks of tonsillitis the stomach would appear to be atonic and the hunger contractions would disappear At these times appetite was lost, and food put into the stomach through the fistula produced nausea

Similar observations were made in the case of Tom the man with a gastrostomy, who was studied by Wolf and Wolff From time to time under the influence of emotion Tom's mucous membrane changed markedly in appearance When he was discouraged or upset nervously the gastric mucosa became pale, and the secretion of acid was lessened When he was angry resentful, anxious or sleepless, the volume and the acidity of the gastric juice rose to perhaps three times normal, and the mucous membrane became turgid and red Worry caused heartburn The physiological state of the stomach and the appearance of the mucosa did not have any influence on Tom s appetite

During periods of hyperfunctioning of the stomach the mucosa often took on the appearance that it has in a case of hypertrophic gastritis That this was not due to any inflammation was shown by the fact that the abnormality would disappear shortly after Tom cooled off emotionally Anything which caused hyperemia and engorgement of the mucous membrane with hypersecretion, was likely to produce this picture of hypertrophic gastritis

During health the pinching of the mucosa of the stomach between the blades of a forceps or pressure on it did not produce much distress or pain but when the mucosa was engorged with blood or edematous pinching caused severe pain Intense contractions of the stomach sometimes caused nausea

Schindler has described acute gastritis and has expressed his belief

Acute Indigestion Due to Fatigue

Short attacks of indigestion sometimes with diarrhea and abdominal pain are seen not infrequently in campers and mountain climbers Often the trouble seems to be due to the eating of too much food when the person is greatly fatigued At such times the digestive forces seem to be paralyzed and food can then pass through the stomach and bowel almost unchanged

Anyone who knows anything about the care of horses knows that the animal that has traveled far in a day must not be given food or drink for two hours or more after coming in Unfortunately a man traveling through the mountains is often much more careful of his horse than of himself

In such an acute spell there may be a feeling that the food has not left the stomach and is not going to leave it There may be nausea and finally vomiting and perhaps some diarrhea There may be headache muscular soreness slight fever a coated tongue a bad taste in the mouth a disgust for food a bad breath colicky pains and perhaps a considerable degree of prostration All this distress may pass off in twenty four hours or some of it may remain for a few days For several days after the episode there may be epigastric pain on eating

Diagnosis of Acute Infectious or Toxic Gastritis

Usually in cases of acute indigestion with abdominal pain the essential thing is to rule out an attack of perhaps appendicitis or cholecystitis or the passage of a stone through the ureter Sometimes within a day or two it will be obvious that the patient is coming down with some infectious disease Marked tenderness and rigidity of the abdominal wall will speak for the presence of some severe condition which may require surgical treatment The urine should be examined and search made for red blood cells pus cells or bacteria In women the pelvic organs must be examined The trouble may be due to acute salpingitis a tubal pregnancy or a miscarriage In older persons one must think of the possibility of a small cerebral accident Purgatives must not be given until the physician is sure that he is not dealing with acute appendicitis or acute intestinal obstruction

Treatment of Acute Infectious or Toxic Gastritis

If vomiting is severe and prolonged it will be advisable to give fluids intravenously Water can be given by mouth in order to wash out the

only a few hours The clinical picture, once seen, will never be forgotten It is that of a person who if seated on the toilet, is vomiting on the floor or, if vomiting into a bowl is voiding incontinently on the floor Similar epidemics with milder symptoms are now and for a long time have been frequent Usually they are considered to be due to food poisoning

These epidemics sweep suddenly through dormitories, hospitals barracks attacking perhaps 50 per cent of the personnel at one time Although for a few hours the disease can be most distressing and embarrassing the attack usually is of such short duration that little attention has been paid to the problem of its etiology

The epidemics usually tend to come in the autumn months A virus cause has been claimed Some writers have assumed that the trouble is due to a gastroenteritis while others including the writer have been impressed by the fact that in most cases there is neither soreness of the abdomen, bloating pain nor fever The impression left is that a virus must empty the digestive tract by affecting in some way the nervous system of the bowel

In most cases intestinal contents run out of the *rectum easily without* any cramping There is usually no great rise in temperature or in the pulse rate The intestinal contents are not irritant to the anal ring Usually the next day the only remainder of the spell is some fatigue and much sleepiness, both to be expected after so strenuous a session In some of the patients the diarrhea continues for several days or even longer

If there had been any enteritis, and if the lumen of the bowel had been full of bacteria, recovery could hardly have taken place so suddenly without any residue of soreness Futhermore the epidemics do not seem to leave in their wake any cases of chronic diarrhea

Treatment —Usually there is no time for any treatment, and the attack is over before much can be done about it The patient is too busy to be bothered with treatment

Alcoholic Gastritis

An acute digestive upset following a drinking bout is commonly thought to be due to acute gastritis but many studies with the gastroscope and at necropsy have indicated that this is not necessarily true The vomiting and other distresses may well be due to the *effects of* alcohol on the brain and on all the tissues of the body

drugs are not of much value Better probably is the syrup of lime or a solution of potassium permanganate For phosporus poisoning dilute solutions of potassium permanganate are used For arsenic 4 ounces or 1 o c c of freshly prepared ferric hydrate with magnesia U S P should be given More recently BAL has been used after arsenic poisoning

After the poison has been neutralized or washed out, demulcents such as raw eggs and gruels can be given

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stomach Especially if there is no diarrhea, two 1½ grain (0 1 gm) capsules of pentobarbital sodium (nembutal) or a 3 grain (0 2 gm) rectal suppository of nembutal can be inserted This may quiet the vomiting center and give the patient much needed rest In cases of diarrhea an enema of warm physiological salt solution at bedtime may allow the patient to sleep

After the vomiting has stopped it may help to give teaspoonful doses of bismuth subcarbonate or subgallate or kaolin Sometimes a dose of castor oil will help but it should not be a routine prescription in such cases Naturally if the diarrhea should continue a bacteriologist should search the stools for some of the common dysentery-producing organisms and a parasitologist should look for amebae

Acute Phlegmonous Gastritis

This is a diffuse or localized inflammation of the gastric wall Fortunately it is a rare disease It appears usually to be due to bacteria of some type The condition may be associated with gastric ulcer or gastric carcinoma or it may be associated with some severe infectious disease The whole gastric wall may be thickened and full of little abscesses and patches of thrombophlebitis

The symptoms are those of a severe acute abdominal infection There may be chills, abdominal pain fever and vomiting There may be all the signs of an acute abdomen The prognosis is bad and most patients die of the disease Because the etiology is not well known and the disease is fulminating little is known about what treatment should be tried

Gastritis Due to Swallowing of Poison

In many cases of toxic gastritis the best way of helping the patient is quickly to wash out the stomach with a large stomach tube and plenty of warm water If the poison was an acid substance the stomach should be washed with dilute alkali such as a solution of sodium bicarbonate or magnesia If the poison was alkaline one can use a dilute solution of hydrochloric acid

In the past it has been recommended in cases of phenol poisoning to wash the stomach with a 10 per cent solution of alcohol or a solution of magnesium sulfate but the studies by Macht (1915) Wilbert (1916) Carl and Brown (1906) and Dunn & Perley (1931) indicated that these

some tiny erosions The tissues below the epithelium were infiltrated with plasma cells

Nothing really definite appears to be known about the cause of this type of gastritis there are a number of hypotheses but not many facts of observation Some gastroscopists are beginning to wonder if superficial gastritis is worth talking about or if it is really a disease

It is hard to say what the symptoms are, granting that there are some produced by the lesion Because the mucous membrane of the stomach is practically without sensation it is hard to see how small deviations from normal could ever produce any distress Naturally the patients who are gastroscoped all have some symptoms of indigestion and always there is the temptation to ascribe these symptoms to the lesion found

The experienced gastroenterologist who has his feet on the ground is slow to ascribe the symptoms of indigestion to superficial gastritis because he knows that the lesions have been found in healthy students or soldiers who had no symptoms at all It probably is true that lesions of gastritis are found more commonly in persons who are complaining of indigestion but this does not prove a relationship between lesions and symptoms The symptoms complained of can be due so easily to a neurosis or to some disturbance in some part of the digestive tract or in the body outside of the stomach Analysis of gastric contents does not help because one can find any degree of acidity in these cases

As Schindler has noted the condition may disappear rapidly and completely with or without treatment It is possible that it may be a forerunner of atrophic gastritis

Treatment —The treatment that has been recommended is rest plus a liquid diet and perhaps a washing out of the stomach every morning for some time The patient should be taught to wash the stomach himself After a while the diet should be enlarged but roughage should be banned There are no drugs that can be counted on to affect the situation It may help to clean up the mouth to treat pyorrhea and to remove other foci of infection Actually nothing definite is known about treatment.

Chronic Atrophic Gastritis

Schindler has felt that this condition must be the end result of chronic inflammation but today a number of gastroscopists and others feel that in many cases the atrophy has probably resulted from causes unknown They see no reason for assuming that inflammation entered into the

Chronic Gastritis

In the old days before the coming of the flexible gastroscope the term chronic gastritis was used often by physicians as a cloak for ignorance. Some made this diagnosis whenever they found an increased amount of mucus in the gastric contents; others when they found achlorhydria or achylia. Many textbook writers grouped under the heading of gastritis all these cases of poorly understood indigestion due perhaps to overeating, to the drinking of alcohol, to cardiovascular-renal diseases or to chronic infectious diseases of various kinds.

Some physicians thought that gastritis was due to dietary indiscretions, to overeating, to the habitual bolting of food or to the eating of heavily spiced or badly cooked foods. Some attributed gastritis to the drinking of ice water or iced liquids of various kinds, others to the taking of drugs such as digitalis, iodides, salicylates or acetylsalicylic acid (aspirin).

In recent years since Schindler and Wolf devised the flexible gastroscope there has been a tremendous increase in the interest taken in the subject of gastritis and much has been written on the subject. At last opinion on some phases of the subject appears to be crystallizing, but there still remain differences of opinion and questions that have not been answered. There is no more any question about the fact that the gastric mucosa in many persons appears to be abnormal, but just why this abnormality came or what produced it or what symptoms are being produced by it are questions not yet answered.

According to Schindler and others gastritis can be divided into three main groups, (1) chronic superficial gastritis, (2) atrophic gastritis and (3) chronic hypertrophic gastritis.

Chronic Superficial Gastritis

This may be patchy and may occur in any part of the stomach, but it is met with more frequently in the body of the stomach than in the pars pylorica. According to Schindler the three characteristic signs are (1) patchy redness or hyperemia or reddening of the tops of the folds, (2) edema producing a watery appearance and (3) exudation. Some sticky mucus may be observed. Small mucosal hemorrhages and erosions are seen frequently. A biopsy made by Dr Ortmayer in a case of severe superficial gastritis showed a normal appearing surface epithelium with

Treatment—In cases of atrophic gastritis the giving of hydrochloric acid is seldom necessary or advisable Usually it does not appear to do any good even when the patient has a little diarrhea If it is given at all it should be given in doses of perhaps ½ teaspoonful of the U S P dilute acid This should be taken well diluted with meals Always after taking the acid the teeth should be rinsed and particularly the upper incisors Otherwise the acid will take off the enamel from the lingual surface of these teeth

Especially in those many cases in which the patient s digestion is satisfactory it would seem foolish to modify the diet, especially as no one really knows how it should be modified

Relation of Atrophic Gastritis to Pernicious Anemia

It is not yet clear what relation there is between the atrophic gastritis of a primary anemia the achylia after histaminic stimulation, the liver changes and the destruction of the nerve tracts in the spinal cord There are many reasons for believing that the disease is inherited and that different members of the family can inherit one or more parts of the syndrome without all of the others Thus many persons in a family will have the achlorhydria without the anemia or the cord changes Others can have early gray hair and slight cord changes and no anemia

Chronic Hypertrophic Gastritis

In chronic hypertrophic gastritis there is infiltration of the gastric mucosa and proliferation so that the folds become large and thickened The diagnosis of hypertrophied rugae often can be made by the roentgenologist (Fig 2) In healthy persons the mucous membrane as seen through the gastroscope is glistening and smooth but in cases of hypertrophic gastritis it has a velvety dull, spongelike appearance Sometimes there are areas in which the mucous membrane has a nodular appearance or a cobblestone surface Such changes are found most frequently in the body of the stomach but they may extend into the pars pylorica There may be patches of acute inflammation with hemorrhage and ulceration Little ulcerations may come and go from day to day

At necropsy or operation one finds proliferation of the surface epithelium the gastric crypts are elongated some cysts may be found and

process In some cases the atrophy is associated with a primary anemia or a sprue-like disease or with various types of undernutrition In older persons it may be the result of purely senescent changes It is known that in men and women the percentage of persons with achlorhydria increases with age Severe atrophic gastritis is found also with Hodgkin's disease and leukemia

The gastroscopic picture is that of a thinning of the mucosa and a change of the color to a greenish gray The normal folds tend to disappear Ruffin once pointed out that if the gastroscopist pumps in too much air and distends the stomach until the folds disappear, he may be deceived into thinking that he is dealing with an atrophic mucous membrane The disease may be patchy or the entire gastric mucosa may be atrophic In advanced cases the blood vessels of the stomach show plainly through the thin overlying mucosa

Microscopically there is a transformation of the superficial epithelium into one resembling that of the *small bowel* The gastric glands are replaced by typical Lieberkühn glands Erosions may occur At necropsy the gastric mucosa is found to be thin and smooth with the folds partly gone

Symptoms —Again it is hard to say whether atrophic gastritis often produces symptoms and if it does no one knows what these symptoms are Certain it is that often it does not produce any recognizable symptoms Not infrequently the patient with advanced primary anemia and a markedly atrophic mucosa does not complain of indigestion but rather of distresses in the legs Many persons with atrophic gastritis and achlorhydria still have good health and the digestion of an ostrich

According to Schindler in one third of these cases of atrophic gastritis the stomach does not respond to stimulation with histamine In other cases there is normal acidity and occasionally even hyperacidity In all cases of gastritis with a lack of response to histamine the blood should be studied to rule out the presence of a primary anemia

Prognosis —Persons with an atrophic gastric mucosa are more than normally subject to cancer of the stomach The incidence of carcinoma of the stomach is higher in patients with primary anemia than in those without it

Cases of pernicious anemia have been reported in which, after the patient had been for some time treated with liver extract the gastric mucosa regained its normal appearance There has even been some return of the secretion of acid In a considerable percentage of cases of primary anemia there is no atrophic gastritis

the symptoms to resemble those of gastric ulcer From time to time there may be hematemesis In many of the worst cases it is impossible for either the roentgenologist or the gastroscopist to say whether or not carcinoma is present

The Course of the Disease and Prognosis—Chronic hypertrophic gastritis may be present for many years without causing the patient any great discomfort In other cases it will produce a severe syndrome requiring surgical intervention Sometimes the surgeon must operate and resect part of the stomach because even at operation he cannot tell what kind of a lesion he has in his hand only the pathologist can tell In the worst cases operation is almost out of the question because the whole stomach is involved in the process

Treatment—If the patient is not operated on, he should be put on a diet, and often this must be of the type that is used for ulcer From time to time in the worst cases the patient should be put to bed on a Sippy type of regimen Sometimes this will cause the symptoms to disappear All alies may have to be used Schindler used roentgen therapy in a few cases with betterment It may change the condition into one of atrophic gastritis

Postoperative Gastritis

Schindler has stated that following gastroenterostomy or subtotal gastrectomy gastritis will always come if the stoma does not work well This type of gastritis is different from the others that are seen in the stomach before operation After operation they may be any type of gastric change but the atrophic ones are rare Hemorrhagic areas are common

Mixed Types of Gastritis

Puzzling for the classifier of disease is the occasional presence of atrophic and hypertrophic types of gastritis side by side in one and the same stomach Small hemorrhages are seen often with various types of gastritis and even in a normal mucosa Purpuric patches may be seen Sometimes the mucous membrane will bleed more readily than normal when touched with the gastroscope, and according to Schindler this suggests the presence of superficial gastritis Edema may be seen sometimes It produces the picture of a soft soggy jelly-like pale mucosa with increased highlights Small erosions may be seen here and there

there may be much lymphocytic infiltration and edema The lymph follicles are enlarged

Symptoms —It is not certain that even this marked deviation from

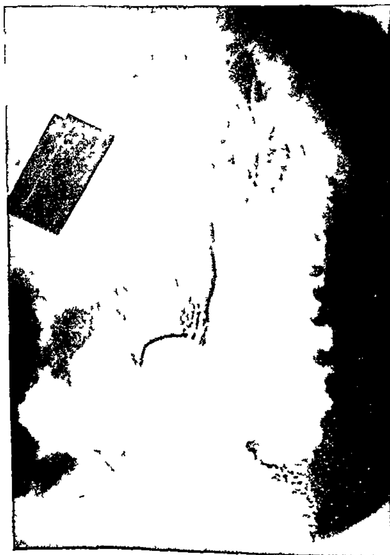


Fig 2 Marked hypertrophy of the gastric mucosa without apparent ulceration

the usual picture will always produce symptoms but often one would expect it to do so especially when there is some acute ulceration and inflammation of the mucous membrane Sometimes then one would expect

small amount of a thick mixture of barium, he can learn a great deal about the mucosal relief of the stomach Often in this way, or even with an ordinary barium meal the roentgenologist can recognize the presence of hypertrophied rugae (Fig -) or a tendency to polyposis He may note also signs of atrophy or dryness of the mucosa Unfortunately for the roentgenologist who would diagnose gastritis much of the appearance of the mucosal folds depends on the tonus of the muscularis mucosae For this reason a roentgenological diagnosis of hypertrophic gastritis can be wrong Katsch and Berg felt that marked widening of the folds in the stomach together with tortuosity and rigidity should be looked on as suggestive of gastritis In some of the cases it is impossible to rule out carcinoma Some roentgenologists have described a corn cob relief a warty granulated appearance or a cobble stone appearance Kirklin has noticed this picture most frequently in the pars pylorica Another term used is gastritis pseudopolyposa Because of contractions of the muscularis mucosae the picture along the greater curvature of the stomach may have an irregular jagged saw tooth appearance This never appears along the lesser curvature

One would not expect to be able to see with the roentgen rays the changes of superficial gastritis and there are difficulties in the way of recognizing the presence of atrophic gastritis With the latter condition if there is no damage to the muscularis mucosae the folds of the stomach may appear to be normal The roentgenologist often can diagnose severe ulcerative gastritis with giant rugae Something may be learned by him also about the pliability of the gastric wall and this may help in ruling out the presence of carcinoma He can oberve how waves of peristalsis go through a region that appears to be abnormal

Diagnosis of Gastritis by Analysis of Gastric Contents

Something may be learned about the condition of the gastric mucosa by observing the amount and quality of the mucus which is obtained through the stomach tube In the future something may be learned from correlating these observations with the gastroscopic findings

When Should the Physician Send a Patient for Gastroscopy?

Naturally, at first as soon as the flexible gastroscope was made available to many physicians there was a tendency to use the instrument on

With hypertrophic gastritis there may be the formation of pseudopolyps True polyps are also found in the stomach

Complications of Gastritis

It seems probable that in many cases chronic gastritis is associated with enteritis but diarrhea seldom is a symptom According to a number of writers chronic gastritis is the soil in which ulcer and carcinoma develop and there is evidence in favor of this view Some, however, do not agree with this After all it is only rarely that we know what the gastric mucosa has looked like before a cancer develops

The Significance of the Finding of Gastritis

Naturally, before blaming a little gastritis for the patient's indigestion every effort should be made to rule out other causes such as digestive neurosis, food sensitiveness cholecystitis a diaphragmatic hernia, hepatitis or a fibrositic ache in the abdominal wall One should be particularly loath to ascribe feelings of nervousness, fatigue and lack of energy to gastritis because they are seen so commonly in nervous and constitutionally inadequate persons After the gastroscopic report comes to hand saying that the patient has gastritis, it will take all the clinical wisdom the gastroenterologist has to know whether to attach any significance to it, or whether even to mention it to the patient, who may be alarmed to no purpose The next question is should there be strenuous and prolonged treatment? In most cases probably not If some trial of a smooth diet with interval feedings and perhaps alkalies helps, well and good If it does not help in a few weeks, it had probably better be given up

In cases of pseudopolyposis of the stomach the physician should know that many patients with this go for years without coming to any bad end A single polyp may disappear after a year or two Patients with markedly hypertrophic rugae can go for years without trouble The patients that one should worry about most and treat carefully are those with an ulcerative type of hypertrophic gastritis Cases have been observed in which this condition proved to be a forerunner of general carcinomatosis of the stomach

Can Gastritis Be Diagnosed by the Roentgenologist?

Especially when the roentgenologist uses the technic of Berg Forssell and others in which the examination is begun after giving only a

of pain and the gastroscopist will notice that he cannot distend the stomach properly the air evidently is escaping On roentgenological examination air *will be found under the diaphragm but at operation the* surgeon will be unable to find any rent in the gastric wall

Contraindications to Gastroscopy

Gastroscopy should not be attempted in the presence of (1) obstruction in the esophagus or at the cardia, ( ) aneurysm of the aorta (3) corrosive or phlegmonous acute gastritis (4) extensive cancer of the stomach and (5) cirrhosis of the liver with possible varices in the esophagus The procedure is not too safe in cases of angina pectoris severe kyphoscoliosis and in dyspnea from any cause

Comparative Value of Roentgenological and Gastroscopical Studies of the Stomach

A number of studies have been made to compare the accuracy of the roentgenologist and the gastroscopist in diagnosing gastric lesions Ricketts and Pollard (1946) analyzed the records of 1 97 patients who had been studied by both groups of workers They excluded cases of duodenal lesions and cases in which symptoms returned after operations on the stomach In 17 cases in which both examinations were negative no positive clinical diagnosis was made in 60 in the other 11 cases the clinical diagnoses varied widely In the 355 cases with conflicting gastroscopical and roentgenological diagnoses in 46 the gastroscopist failed to find the lesion reported by the roentgenologist In the 309 cases with negative roentgenological reports and positive gastroscopical findings there were, as one might have expected many (69) cases of chronic *gastritis a condition not easily recognizable by the roentgenologist* In 3 cases in which the gastroscopist and the roentgenologist had agreed on a diagnosis of carcinoma the histological examination showed a tumor like type of gastritis

In an excellent paper Moersch and Kirklin (1946) compared the results of gastroscopical and roentgenological diagnoses in 100 borderline and particularly difficult cases of what proved at operation or necropsy to be carcinoma of the stomach Obviously this type of study is most valuable because it is in just this type of case that the clinician most needs help It should be remembered also that the men who made these examinations had the sort of skill and good judgment that comes from an *enormous experience It is all the more sobering therefore, to learn that*

practically every patient with indigestion who would submit to the procedure Today this does not look like good medical practice, and the average gastroenterologist is sending only a few of his patients to the gastroscopist Practically all are sent first to the roentgenologist, and if his report on the stomach explains the clinical picture or agrees with the clinician's impression that will be the end of the matter

Much depends on the ability and experience of the clinician If he is a good diagnostician in his own right, and if he has recognized the well known syndrome of some neurosis probably he will be satisfied with a negative report from the roentgenologist, and he will not go on demanding from him and the gastroscopist the diagnosis of some organic disease Only in a certain few cases will he be dissatisfied with a negative report from the roentgenologist and only in these cases will he remain uneasy about the diagnosis

The patients with such problems whom he will send for gastroscopy, are likely to belong to the following classes 1 Older persons with a short history suggesting carcinoma and a negative roentgenologic report Perhaps they have vomited some blood and the physician then will be uneasy until he knows whence it has come 2 Persons with gastric lesions the nature of which the roentgenologist could not determine to his satisfaction Often in such cases the roentgenologist will ask that the patient be examined by the gastroscopist 3 Patients with a gastric "ulcer" may have to have it looked at by the gastroscopist to see if it looks more benign than malignant or if it shows good signs of healing after a few weeks of treatment 4 Patients with an apparently benign tumor or some polyps or a patch of what looks like hypertrophic gastritis often must be checked by the gastroscopist 5 Patients with what the clinician suspects may be gastritis perhaps because of the presence of achlorhydria or a large amount of mucus in the gastric juice 6 Patients who remain uncomfortable after gastroenterostomy or partial gastrectomy In their case the gastroscopist may be able to tell something about the gastric mucosa or the stoma or even the jejunum beyond it

Gastroscopy is also discussed in Chapter IIX of this volume

Is Gastroscopy With the Flexible Gastroscope Dangerous?

In the hands of a well trained gastroscopist the procedure is not attended with much danger However case reports are appearing in the literature of a peculiar condition in which the gastric wall appears to be injured enough to let air go through The patient will complain

Kirklin often has based his diagnosis of gastritis on the presence in certain areas of irregular, hypertrophic mucous folds In other areas he may see wartlike granulations In attempting to differentiate carci noma and gastritis Schindler has pointed out that the nodules on the surface of a benign tumor are regularly granular and rather uniform in size whereas in malignancy they are irregular and variable, some very large and some small In hypertrophic gastritis the nodes are not so stiff and no solid tumor like protrusion is observed

A fine analysis of the successes and failures of the gastroscopist is that of Benedict (1947)

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the gastroscopist was wrong in 20 cases and the roentgenologist in 4 cases In only 5 cases did the gastroscopist fail to see a lesion, while the roentgenologist failed to see anything wrong in 13 cases In 11 cases the gastroscopist made an error and reported hypertrophic gastritis, the roentgenologist made the same mistake in 10 cases In 5 cases what looked to the gastroscopist like a benign gastric ulcer proved at operation to be malignant The roentgenologist made a similar mistake in 14 cases

Important is the fact that in 10 of the cases the surgeon at operation was unable to say what the lesion was, and the problem had to be put up to the pathologist Curiously in one case the surgeon for a while was unable to find the lesion that had been seen by the gastroscopist As one might have expected it was in just these cases in which the surgeon was puzzled that both the gastroscopist and the roentgenologist had their greatest difficulty in making a diagnosis They guessed right in only 2 of the 10 cases

It is noteworthy that in 30 of the 100 cases of puzzling carcinoma the roentgenologist asked that gastroscopy be performed In 19 of these the roentgenologist had diagnosed carcinoma and in only 2 of the 19 was the lesion not recognized also by the gastroscopist In 8 of the 30 cases the roentgenologist had been unable to see a gastric lesion or to be sure of what he saw In all of these 8 the gastroscopist recognized a carcinoma In the 3 remaining cases both the roentgenologist and the gastroscopist failed to diagnose the carcinoma that was present Naturally the hardest type of carcinoma to diagnose is often the linitis plastica type in which the stomach is done over in cancer cells

All of this shows that the internist the roentgenologist and the gastroscopist should work together in the most friendly and co-operative way in order to supplement one another's diagnostic efforts

Both Moersch and Kirklin pointed out that in puzzling cases it is always well to repeat the examination The gastroenterologist also if he is to save the patient's life must in some cases realize from the nature of a short history and perhaps the age and condition of the patient that he must keep sending the man or woman back again and again for examinations and if these are not entirely satisfactory he must order a surgical exploration He just must not temporize and lose time

Moersch reported 100 cases of gastritis confirmed at operation by inspection or biopsy His diagnosis was correct in 80 cases and wrong in 20 In 1 of the cases he had diagnosed carcinoma The presence of a little blood in the stomach did not help in making the diagnosis, since it can be found with either gastritis or carcinoma

will diagnose a small diaphragmatic hernia while other will feel that the shadow immediately above the diaphragm represents only a little enlargement in a congenitally short esophagus (Fig 4) In such cases



Fig 3 Esophageal hiatal hernia with a third of the stomach in the thorax There was a traumatic ulcer on the greater curvature at the place where the stomach was pinched

Diaphragmatic Hernia and a Short Esophagus

Herniation of a part of the stomach through the diaphragm is being found more and more frequently now that it is being looked for Often, if it is to be found, one must suspect from the story that a hernia is present and must ask the roentgenologist to look particularly for it, if he examines the patient only in the standing position behind the roentgenoscope he is likely to miss it If he knows that it is suspected, he will have the patient lie down on the horizontal table and will ask him or her to strain so that some of the stomach can go up into the thorax

At operations Harrington has made a custom of examining the esophageal hiatus, and in a high percentage of patients he has found it large enough to admit a finger or two In all but a few cases the hernia is congenital in origin and due to the presence of this large hiatus (Fig 3) In other cases there is a rent in the diaphragm usually produced by an automobile accident in which the person smashes the steering wheel with his thorax

A diaphragmatic hernia must be thought of in all cases of puzzling epigastric pain and especially pain which comes after eating a large meal, after lying down soon after dinner or on leaning over to tie shoes Sometimes there will be a little dysphagia Especially when a large amount of the stomach goes up into the thorax, there may be some shortness of breath and symptoms suggesting heart disease There may be some palpitation or a sense of fullness in the chest Rarely there will be attacks of smothering, or there may be anemia or hematemesis due to the formation of an ulcer in the bit of stomach caught and compressed in the hernial ring Occasionally in bad cases the splenic flexure of the colon also will go up into the thorax

The diagnosis often is puzzling even after the hernia has been found because the symptoms will resemble those of coronary thrombosis and angina or sometimes those of cholecystitis with stones Worse yet, one may find, in addition to the hernia signs of cornary disease or cholecystitis or both Then the clinician will need all his experience and wisdom to tell how to apportion the symptoms among the several diseases Puzzling also may be the question of what to do in the way of treatment Obviously it will do no good to operate on the hernia, if most of the symptoms are due to coronary disease, and it will do little good to remove the gallbladder if the symptoms are all due to the hernia

In many cases today there is a difference of opinion among roentgenologists and clinicians in regard to what shows on the films Some

patient In some cases esophagoscopy is advisable in order to establish the presence or absence of ulceration at the cardia

Prognosis

The patient who has just discovered that he has a diaphragmatic hernia naturally wants to know about his future If he is not operated on what will happen As one would expect some of the hernias get larger as time passes but, especially if the patient reduces weight or remains thin he or she may live for years without getting any worse Especially if the hernia is small and the symptoms mild or perhaps all due to a neurosis it would seem wise to wait and once a year or so to check the thing roentgenologically to make sure that it is not enlarging The writer s impression is that most of them do not enlarge with time and few of them are being operated on now

Treatment

Before starting any treatment the physician must make up his mind from talking to the patient how much of the distress if any is due to the hernia As already noted if the hernia is small and the symptoms mild or perhaps not due to the lesion operation should not be considered If as often happens the patient is stout with a large abdomen a symptomatic cure may be worked through dieting and the reduction of weight

When the esophagus is decidedly short operation will be impossible In some cases, in which there is a large traumatic hernia it may help first to evulse the phrenic nerve on the affected side so as to keep the diaphragm from cramping down This alone may help enough or later the rent in the diaphragm can be repaired Fortunately in good hands the mortality rate of the operation is low

Carcinoma of the Stomach

In men the stomach is perhaps the commonest site of cancer In most clinics the disease is found about three times as often in men as in women It is found in from 1 5 to 4 0 per cent of persons coming to necropsy Although cancer is largely a disease of the later years of life physicians must never forget that it can appear even in the third and fourth decades

it is well to repeat the roentgenological examination once or twice and then, if doubt remains to have an expert esophagoscopist examine the



Fig 4 Short esophagus with some of the stomach in the thorax There was an ulcer at the esophagogastric junction

a characteristic translucent appearance Microscopically the epithelial tissues are seen to be replaced in large part by structureless gelatinous material containing the remnants of cells The tumors tend to spread widely through all the coats of the stomach and out into adjoining organs

A squamous cell carcinoma sometimes is found at the cardia where it arises from esophageal epithelium

It is an interesting fact that gastric carcinomas generally stop at the pyloric line They do not seem to be able to invade the duodenum but they sometimes grow into the colon and thus lead to the formation of a gastrocolic fistula

As the tumors grow to large size they often fill the lower end of the *stomach and block the outlet The mucous membrane adjoining the* tumor almost always shows inflammatory changes

Sooner or later metastasis appears first perhaps in the nodes along the curvatures of the stomach and then in the liver This organ often becomes so full of carcinoma cells that its enlargement is the feature which strikes the physician's eye when he examines the patient The lesion in the stomach may be so small that at necropsy the pathologist thinks for a time that he is dealing with primary carcinoma of the liver

Early Cancer of the Stomach as It Is Found in Ulcers—Now what do the earliest lesions look like when they are discovered at operations or necropsies? Rarely one finds a small adenomatous plaque and occasionally this will have grown out over the surface of the mucosa to look something like an old leaf Occasionally one finds a polyp with malignant changes at some point and occasionally one finds a patch of what looks like hypertrophic or ulcerative gastritis Probably most commonly one finds an ulcer with perhaps a little thickened place here and there on the edge Microscopic study of these thickened places will show *either frank carcinoma or glands in which the cells contain disproportionately* large nuclei which stain heavily with hematoxylin

Because years ago some pathologists expressed doubt as to the significance of the histological changes found in these small lesions I reviewed with MacCarty the records of 100 persons who had been operated on at the Mayo Clinic and had been found to have some of the smallest ulcer like cancers ever encountered If ever mistakes in diagnosis had been made they should have been made in this group of cases Actually so far as I could see there could not be much question about the diagnosis because at the time of operation in a third of the cases metastasis could be demonstrated in the lymph nodes or liver and within a year

of life In . 086 cases of cancer of the stomach seen at the Mayo Clinic 3 7 per cent of the patients were less than 35 years of age and 19 6 per cent were less than 45 Obviously then the physician must be on the watch for this disease even when the patient is in his thirties

Pathology

In Welch s 1 300 reported cases the distribution of the growth in the stomach was as follows pyloric region 791, lesser curvature 148, cardia 104 posterior wall 68 the whole or the greater part of the stomach 61 multiple lesions 45 greater curvature 34, anterior wall 30 fundus 19

The commonest type of gastric cancer is the adenocarcinoma This forms usually a soft often a papillomatous mass which projects into the lumen of the stomach *Microscopically* it consists of tubular structures lined with cells which as MacCarty has emphasized, are distinctly abnormal Here and there they break through the lining membrane and invade the surrounding tissues showing definitely that the change is a malignant one Furthermore in many places the lumen of the tubules is completely obliterated by the overgrowth of the cells

The medullary carcinomas appear as soft grayish vascular masses, which grow rapidly into all the coats of the stomach They ulcerate easily and metastasize rapidly The cells are spheroidal in type and they grow aberrantly and without much framework Naturally there are many transitional forms between the typical adenocarcinoma and the typical medullary carcinoma

The scirrhous cancer is dense hard and slow growing A small one sometimes will block the pylorus either mechanically or by causing contraction of the muscle there Sometimes the growth invades the muscle and replaces it in such a way as to form a replica of the stomach in cancer cells This produces what is called a leather-bottle stomach or linitis plastica In one such case at the City Hospital in San Francisco, in which the young woman came to necropsy the pathologist could not be sure that the stomach was abnormal until he saw the sections under the microscope Sometimes such stomachs become contracted and small, and there may be so much fibrous tissue present that the microscopist has to search through many fields before he can find typical cancer cells (see section on Linitis Plastica)

The gelatinous or colloid really mucus forming carcinomas have

wanting What is unfortunate is that most of the men, who wrote on the subject and derided the idea that cancer could originate in an ulcer failed to see the essential point which was that the question which frequently faces the physician *is not*, *is this ulcer that we have found going to become cancerous* but is it already cancerous? ' This is the puzzle to which neither clinician nor roentgenologist nor gastroscopist can always give a sure answer They can guess right much of the time but every so often they will hear that a patient who had a typical ulcer" with a high gastric acidity was found at operation or necropsy to have a cancer Perhaps their confidence in their diagnostic ability will be shaken, when at operation they see the *surgeon* or pathologist unable *to make a diagnosis after* he has the lesion in his *hand* The larger a physician s experience and the oftener he sees cases in which every rule of diagnosis by which he works has been broken the less confidence he will have in his ability always to tell a benign from a malignant lesion Usually after a while he refuses to treat medically a gastric lesion of any kind unless the patient will remain under close observation for a *time long* enough to make *fairly certain* that the danger *of cancer is past (see Alvarez 1931 1946)*

Obviously in a high percentage of cases perhaps over 90 per cent the roentgenological diagnosis of carcinoma of the stomach can be made with ease and certainty The lesion is a tumor which produces a filling defect or it alters the configuration of the gastric mucosa or it makes the wall of the stomach rigid so that waves cannot travel normally The big problems *of diagnosis* come when the *lesion looks like* an ordinary ulcer or a patch of *ulcerative* gastritis or a polyp

If for years the patient has been suffering with attacks of hunger pain, and if roentgenological examination shows that he has a gastric ulcer and not a duodenal one then it can be assumed fairly safely that he started with a benign ulcer He has what is commonly termed a long history and this is most important and reassuring If however he is *past middle age and for the first time in his life* is beginning *to have pain* in the epigastrium and indigestion, and *if he* is *found to have* a lesion *in* the stomach he has a short history and this is terribly dangerous The lesion then can be benign but the chances are large that it is malignant and that it was malignant from the start

Years ago I reviewed 100 records of patients with benign gastric ulcer (all the lesions had been *excised and examined microscopically*) and 100 *records of patients* with inoperable *carcinoma of the stomach* (all surgically explored) I have listed these cases in table I first accord

half of the patients, who had submitted to resection of the lesion, had died many of them with obvious carcinomatosis

Years ago Wilensky and Thalhimer studied 48 ulcer-like lesions removed from the stomach and found 7 to be carcinomatous In another case there were carcinomatous changes here and there in the edges of an otherwise benign ulcer Another lesion appeared to be a benign ulcer but adjacent lymph nodes were full of cancer cells Similar puzzling cases have been reported by MacCarty Roscoe Graham reported that Dr Wooley when he went to a museum of pathology and re examined a number of the lesions which in years past had been filed under the label of gastric ulcer found that 1 in 5 showed cancerous changes somewhere along the edge Cleland while studying 1 000 stomachs removed at necropsy found 36 small cancers Five of them were so small that they were discovered only accidentally, 2 were polyps with malignant changes and 3 were small ulcers He also found that *although in 2 of these lesions the malignant change could be detected only with the microscope metastasis had already taken place* Stewart of Leeds who studied 154 lesions that looked like ordinary gastric ulcers found 14 to be cancerous

It is unfortunate that in the last forty years the medical profession has shown great reluctance to accept the idea that carcinoma can develop in the wall of what looks like a benign ulcer and for long many physicians refused to face this possibility Today all busy internist have had so many unfortunate experiences with patients who have come back with inoperable carcinoma a year or two after being treated for gastric ulcer' that they now have to admit that whatever the explanation may be the patient with an ulcer like lesion in the stomach is abnormally subject to carcinoma of the stomach at the time and for the rest of his life Whether he gets the cancer in the wall of his old benign ulcer or whether he gets it de novo in some other part of the stomach is an academic question, the essential point is that in an uncomfortably large percentage of cases he gets it Some pathologists are now suggesting that both the benign ulcer that appears first and the carcinoma that comes later arise in a gastritis the cause of which is as yet unknown

The Essential Point in the Argument —The sad fact is that during the last forty years while physicians have been arguing this point of the exact origin of gastric cancer thousands of patients with a gastric lesion that looked like a benign ulcer have died of cancer Probably half of them would not have died if only the ulcer like lesion had been excised promptly or soon after medical treatment had been tried and found

always become concerned over the person past middle age who comes with a short history and a gastric lesion of any kind

Importance of the Problem of Early Diagnosis

That the problem of diagnosing early carcinoma of the stomach is far from an academic one can be seen from the fact that during the five years from 19 0 to 1924 inclusive - 018 patients with the disease were seen at the Mayo Clinic In one half of these cases the disease was hope

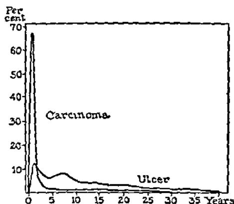


Fig 5 Percentage distributions showing the marked difference in the duration of symptoms in patients with ulcer and cancer of the stomach

lessly advanced and the patient had to be sent home In the other half of the cases the situation seemed hopeful enough so that the abdomen was explored but again in half of the cases in this group nothing could be done Hence in only about a fourth of the cases seen at the Clinic could the tumor be removed with any prospect of cure Still sadder is the fact that today after thirty years of effort to get physicians to diagnose and treat this disease more promptly the situation remains about as bad as it ever was The percentage of resectable lesions seen is not rising to any great extent

The Worst Difficulty —In many cases of course no one is to blame for this situation because the disease grows silently for perhaps several years and by the time the patient has an inkling that he is ill metastasis has taken place and nothing can be done In other cases the blame can be laid at the door of the patient because he put off going to a physician for months after he knew he was ill and in still other cases the blame

ing to the duration of symptoms; in a second according to a code based on my opinion as to the type of history given, that is, whether it suggested the presence of ulcer, cancer, cholecystitis or just a vague indigestion

TABLE I

THE LENGTH OF THE HISTORY OF INDIGESTION

Mos.	Yrs.	100 patients with gastric ulcer operated on	Totals		100 patients with inoperable carcinomas of the stomach explored	Total	
1		h	1		cccv	4	
2		vv	2		cccccc	6	
3					ccccccc obstr. at cardia	8	
4		uvv	3		ccccvu	6	
5		v	1		ccccvv	7	
6		c	1		cccccccccv	11	
7					cvv	3	
8		u	1		ccv	3	
9					c	1	
10		u	1		cc	2	
11					c	1	
	1	ug	2	12	ccccccccccccvvu obstr.	15	67
	2	uuu a u vcc		19	ccccvvuuuu p. anemia	12	9
	3	uuuffv	6		cvuu	4	
	4	uuf	3		u?	1	
	5	uuuvffff	8		u	1	85
	6–9	uuuuuuuuuuuuuvvvvvvvvvffg	23		u u?	2	
	10–14	uuuuuuvvvvff	12		uuu u u u? g	7	
	15–19	uuuuuuvvf	9		uv	2	
	20–24	uuuuuvf	7		ug	2	
	25–29	uuuuf	5		uu	2	
	30–34	uu u g v	4				
	35–39	g	1				
	40	uvv	3				
			100			100	

ABBREVIATIONS: u represents ulcer, v vague, f fair ulcer, c carcinoma, g gall bladder disease, a appendicitis, obstr. pyloric obstruction. Each letter or combination of letters represents a case.

tion or fatigue state. It will be seen at a glance that nearly all of the patients with benign ulcer had long histories, while nearly all of the patients with cancer had short ones. This is shown also in figure 5.

It is obvious from this study that it is possible for some persons to carry on for years with a benign gastric ulcer without getting a carcinoma. One wonders perhaps if such persons have a low susceptibility to carcinoma. That this was not the explanation in some cases was shown by the fact that the patient eventually succumbed to carcinoma of the prostate gland or some other organ. Whatever the explanation for the facts observed, it should be obvious from Fig. 5 that the physician must

goes wrong Perhaps the first abnormality noted is constipation, later there may be some epigastric distress after meals or a gnawing ache or pain with loss of appetite and strength Not infrequently the patient and the physician are not so alarmed as they otherwise would be at these symptoms because they seem to have followed a cold a bit of flu, a slight accident or some mental depression over the death of a relative Everyone hopes that as the effects of the infection or shock or sorrow pass off the patient will get well again

Unfortunately in quite a few cases what with a cutting down on the amount of food eaten or the taking of some medicine the symptoms let up, and the patient thinks he is getting well Then suddenly the symptoms come back and everyone realizes that the man is seriously ill

Then a physician will be consulted and for the next few months a number of prescriptions will be tried out Eventually the family will become alarmed over loss of weight and strength with perhaps an ominous pallor or a little blood may be vomited or a mass discovered in the abdomen Then perhaps the patient is sent to a roentgenologist who *reports* the presence of an ulcer like lesion A Sippy type of regimen is prescribed and again there may be a decided improvement in the symptoms and some gain in weight Finally after a year or more the patient starts rapidly down hill and the advice of a *consultant* is sought

Naturally there are several ways in which carcinoma of the stomach can announce itself depending largely on the location of the growth *and its character* A *scirrhous cancer spreading through the submucosa* can involve the whole stomach without producing any symptoms while a *small tumor* which early blocks the pylorus *will soon announce itself* by producing symptoms of gastric stasis such as *eructation* vomiting sleeplessness constipation and loss of weight A growth near the cardia may soon bring difficulty in swallowing while a big friable carcinoma growing slowly *in the silent area in the fundus* may produce only anemia In many cases the first symptoms are those of metastasis to the liver *lungs or other parts of the body*

The promptness or lateness with which symptoms develop in cases *of carcinoma of the stomach* depends probably to a considerable extent on the sensitiveness or insensitiveness of the patient Older persons who never were very sensitive and who became even *less* sensitive with age can be full of carcinoma without either realizing they are ill or caring to complain of some loss of weight or some feelings of weakness They are like the monkey in the zoo who one day can be jumping

must be shouldered by us of the medical profession, because one or more physicians wasted priceless weeks and months on well intentioned, medical treatment designed to cure a functional indigestion or a supposedly benign gastric ulcer There still are physicians, who do not get alarmed over a short history of indigestion in an older person, and who do not insist immediately on a proper examination Many of those, who know enough to order a good examination, still do not seem to know how dangerous it is to put the patient on medical treatment and then let him drop out of sight They do not seem to know that such a patient can for a time gain weight, lose his indigestion, and then later go down rapidly with generalized carcinomatosis

On the average patients with symptoms of cancer of the stomach still waste a year of invaluable time before they get to a consultant or a surgeon Teachers in medical schools will be partly responsible for this unfortunate situation if they go on showing to their students in the amphitheater not the well nourished healthy-looking man of forty with an "ulcer" in his stomach but the pale, emaciated, apathetic old man with coffee ground vomitus and a fixed mass in the epigastrium It is a sheer waste of time to teach a student to recognize cancer of the stomach in its terminal stages, that does not do any good, and it can do much harm The student must be taught to recognize or strongly suspect cancer in its early stages He must be taught also to grapple with the disease right from the start, and never to let up until a year or more is past and he knows that the patient is fairly safe

Finally physicians young and old must be taught that there is hope for the patient with carcinoma of the stomach Today even the physician with carcinoma in his own stomach commonly will go a year without doing anything about it largely because of his feeling of hopelessness (Alvarez 1931) Sometimes he says "why be operated on when nobody is ever cured?" Actually, as will be shown in the section on prognosis, if a patient with carcinoma of the stomach will only go to a physician or surgeon the minute the typical symptoms begin and if he then can have a gastric resection performed by an able man he has about one chance in three of getting well and staying well His chances are much better than this, if his lesion has a low degree of malignancy

Symptoms

As already noted, the old man or woman with carcinoma of the stomach usually has had a lifetime of good digestion Then something

Diagnosis

As has already been pointed out the essential point for physicians and laymen to remember is that *any disturbance of digestion or any failure in health which appears for the first time in middle life or particularly in late life must be looked on with concern* Even if the patient can ill afford it a roentgenological examination of the digestive tract should be made promptly by an expert If the physician is practicing in a small community he should urge the patient to go immediately to a larger center where a careful examination can be made Only in this way can he be doing his bit to stop the pitiful procession of patients with inoperable cancer of the stomach who now leave the offices of consultants to wend their hopless way to the doors of quacks

The Examination —It may be helpful to remember that some carcinomas of the stomach which cannot be palpated when the patient is lying down and the pylorus is high in the epigastrium can be felt when the patient stands up and the pylorus comes down The patient should stand with the buttocks against a wall the legs well out in front and the body leaning forward so as to bring relaxation to the abdominal wall the examiner should sit before the patient on a low stool Examination in a modern hospital bed with adjustible mattress and springs allows the patient to be relaxed in a half sitting posture which often reveals abdominal masses otherwise missed

Occasionally when there is obstruction at the pylorus peristaltic waves can be seen traveling from left to right in the epigastrium Sometimes the direction of these waves will be reversed temporarily When the growth has gone through the gastric wall to involve the peritoneum the abdominal wall may be too rigid to permit of any satisfactory palpation Perhaps the examiner can find a Virchow node in the left supraclavicular space nodules on the rectal shelf or a large liver full of metastatic growths

Analysis of Gastric Contents —Analysis of gastric contents cannot be expected to have much value in the diagnosis of early carcinoma of the stomach and it cannot be too strongly emphasized that early carcinoma is the only kind worth diagnosing Late carcinoma such as one commonly sees practically always can be diagnosed with ease by the roentgenologist alone Obviously a small nodule or an ulcer perhaps no larger than a twenty five cent piece is not going to destroy or alter the function of many of the acid secreting cells and actually in early cases one can expect any type of report ranging from anacidity due per

about his cage and the next day can be dead with his body riddled with tuberculosis

It must be remembered that there is no particular reason why a change in the character of the cells making up a largely insensitive tissue such as is the gastric mucosa should ever produce any pain or other symptoms. Occasionally by looking up old roentgenograms made of a stomach it can be proved that a tumor was growing there three or four years before it began to produce distressing symptoms. This is particularly likely to be true if the degree of malignancy of the growth happens to be low. In one such case a minister of the gospel tried for three years to cure a good sized cancer of his stomach with faith, and when he gave up and went to a surgeon the lesion still could be removed successfully.

It is a curious puzzle that in not a few cases the patient's symptoms of indigestion began so many years before the carcinoma was found that one can hardly believe that it had begun to grow then. Perhaps the trouble started with a gastritis. In their study of 10 890 cases of carcinoma of the stomach Walters Gray and Priestley found that in 5[illegible] per cent of the cases the first symptom experienced was a vague indigestion, while in 28 per cent the symptoms were similar to those of ulcer. What every physician should know and remember is that in 80 per cent of the patients with hunger pain good relief was obtained for a while with a Sippy type of regimen.

Eleven per cent of all the patients complained only of a vague abdominal distress, 8 per cent just went into a decline and 1 per cent vomited some blood. Eighty-six per cent noticed loss of weight, 81 per cent vomited a little or regurgitated or had other signs of obstruction at the pylorus, 4[illegible] per cent suffered with epigastric pain of an obstructive type, 36 per cent had pain which could have been interpreted as due to ulcer, [illegible] per cent became anemic, 33 per cent were tired and uncomfortable, and 30 per cent suddenly became constipated. This last point about constipation is an important one. The symptom may come because of pyloric obstruction which slows up the current through the digestive tract, or it may be due to the lessening of the amount of food eaten. About a fourth of the patients with gastric carcinoma lose appetite and some get a peculiar distaste for meat. When the loss of appetite persists after the surgical removal of the growth it is an ominous sign suggesting that metastasis had already taken place.

encircles the pylorus may show itself only as a widening of the normal gap between duodenum and pars pylorica



Fig 6 Hourglass stomach due to large benign ulcer on the lesser curvature

Sometimes in order to make sure that the filling defect is not due to spasm the patient must be examined again after the administration of a physiological dose of atropine The true filling defect remains always

haps to the normal process of aging, to hyperacidity. In the early cases with a small lesion the only factor that might conceivably change gastric secretion might be a preexisting or co existing gastritis.

McVicar and Daly who divided more than 2,000 cases of carcinoma of the stomach into two groups of operable and inoperable found free acid in the gastric contents in 53 per cent of the cases in which a resection of the growth was accomplished. Even in the cases of 631 persons with more or less advanced gastric cancer Hartman (1922) found 70 per cent with a hyperacid gastric juice and 0 per cent more with a normal acidity. In their huge group of cases Walters, Gray and Priestley found many cases with a hyperacidity ranging up to 90 units of free acid. On plotting the ranges of gastric acidity in normal persons and persons with small carcinomas of the stomach they found almost no difference between the two distributions.

The presence of blood in the gastric contents occasionally will help in the diagnosis of a gastric lesion and not infrequently the presence of a foul odor arising from the fasting contents on the sides of the stomach tube as it is withdrawn will enable one to make the diagnosis.

Other Laboratory Tests.—In cases of early cancer of the stomach naturally the hemoglobin reading and the red cell count can be normal. In the later stages because of oozing from a friable or ulcerated growth, there may be a decided anemia. An estimation of the erythrocyte sedimentation rate always is helpful. If it is low, one's hopes rise that there is no metastasis but if it is high the prognosis is bad. It is well in all cases to test the function of the liver. If it is badly impaired, one will be fairly certain of metastasis.

Roentgenological Examination.—As has been pointed out earlier in this chapter, the smallest carcinoma usually is to be found in the wall of what looks like a simple gastric ulcer. The larger the ulcer, the more likely it is to be carcinomatous. It can be a typically perforating form of ulcer, and it can even be producing an hourglass contraction (Fig. 6), and still it may be undergoing malignant change. Carman's classification of the changes which are observed in the carcinomatous stomach is so good that I shall follow it here.

Filling Defects.—The commonest and most typical picture with well developed or incurable cancer is the one in which there is a filling defect with ragged edges due to the projection of a tumor into the barium filled stomach. Often a glance at the shadow on the screen is sufficient to enable one to make the diagnosis. A small cancer that

discovery of cancer in the stomach but also generally he will help the physician and the surgeon in deciding whether or not to operate In the first place they will want to know the situation the extent and the mobility of the growth because if it is limited to the pyloric region and freely movable it probably can be excised, if situated in the upper part of the stomach and if it extends almost to the cardia there is only a small chance that it can be removed but if it is fixed to pancreas or liver excision probably will be *impossible or inadvisable* The presence of metastasis sometimes can be suspected from the size of the liver or from

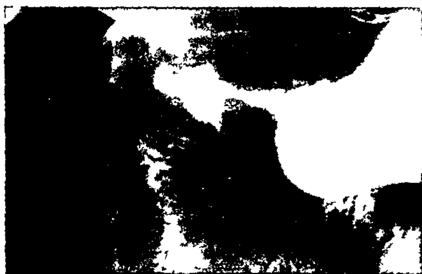


Fig 7 Persistent narrowing of the pars pylorica such as is sometimes mistaken for carcinoma It appeared to be due to a shallow ulcer farther up on the lesser curvature There was also a duodenal ulcer

the irregularity of its upper border Rarely metastatic nodules can be seen in the lung As Moore pointed out the roentgenologist generally is right when he tells the surgeon not to operate but often he is wrong when he reports that the growth is probably removable The difficulty is that the roentgen rays so seldom reveal the existence of metastasis

Puzzling Cases —Occasionally it is difficult for the roentgenologist to distinguish between a marked obstruction due to a high duodenal ulcer and that due to a carcinoma in the pyloric ring Sometimes he can do it only after having the stomach washed out Fortunately in these

the same and the gastric waves do not run over it properly It will be found sometimes on palpation that the filling defect corresponds exactly to the tumor that can be felt in the epigastrium Small tumors sometimes will be missed if the observer fails to watch the first few mouthfuls of barium as they slowly distend the folds of the stomach The pressure of the gas filled colon sometimes will produce defects on the greater curvature of the stomach but for the tyro the commonest source of error is the pressure of the spine against the stomach

Changes in Pyloric Function —The pylorus may gape, or it may be obstructed If it is held open more or less rigidly, the food will pour out into the bowel and the stomach soon will be emptied With such rapid emptying the patients sometimes will have diarrhea The commonest cause is a scirrhous type of cancer With marked obstruction at the pylorus the stomach may contain some barium a day or two after it was taken Carman found six hour stagnation in about 60 per cent of patients with gastric cancer

Changes in Peristalsis —Most characteristic is the failure of the gastric waves to run over the indurated area on the stomach Sometimes the waves can cross the area, but their depth is decreased I have noticed in some cases a bulging of the stomach at the upper edge of the growth just as the waves reached it

Lessened Mobility —During palpation of the stomach under the screen the observer may discover that there is more or less fixation of the viscus This will have a bearing on the problem of operability

Lessened Flexibility —The rigidity of the leather-bottle type of stomach may be detected by the palpating fingers while the patient is behind the screen It may be noticed also as the patient takes the first few swallows of the barium meal

Altered Size and Capacity —The cancerous stomach commonly tends to become shortened and contracted unless the growth is a small one blocking the pylorus, then the stomach probably will be somewhat dilated

Persistent Local Spasm —In rare instances cancer produces spasmodic contractions similar to those seen with ulcer The roentgenologist sometimes will be puzzled by finding a remarkably persistent, funnel-like deformity of the pars pylorica (Fig 7), he may for a few minutes, fear that he is dealing with carcinoma but the smoothness of the outlines will tell him that the defect is due to spasm, and the cause is elsewhere, perhaps in the gallbladder

Operability —The expert roentgenologist will not only report the

and that it is probably malignant Sometimes he can differentiate ulcerative gastritis from carcinoma or he can be fairly certain that a polyp is benign

Test of Medical Treatment—Another method of preoperative diagnosis is to put the patient on a Sippy regimen and watch the lesion carefully for a few weeks using perhaps both the roentgen rays and the gastroscope If the lesion heals quickly and stays healed it is probably benign but there still are a few chances that it will break open again and prove to be malignant

When an older person has a short history and a questionable lesion little time, if any should be spent on testing by medical treatment When however the patient is fairly young and his history of hunger pain is long, the physician is justified in giving him thorough medical treatment before resorting to a surgical operation

Significance of Size of Gastric Ulcers—Four out of five benign gastric ulcers are less than 1 8 cm in diameter the size of a dime and nine out of ten are less than 4 cm in diameter the size of a quarter Studies which I once made on records of 1 3 0 gastric ulcers and cancerous ulcers which were removed at operation showed that on the basis of size alone if the lesion has a diameter less than 2 5 cm or 1 inch the chances are about 10 1 that it is benign When it is larger than this with every increase in size there is a corresponding increase in the probability that cancer is present

Prognosis of Carcinoma of the Stomach After Operation

A remarkable study of the results of surgical treatment of carcinoma of the stomach is that of Walters Gray and Priestley (194) based on a study of 10 890 cases of carcinoma of the stomach in which operation was performed at the Mayo Clinic in the years from 1907 to 1938 inclusive Extremely important was the fact that for the first time in such a study 99 per cent of the patients were kept track of for at least 5 years after operation For the first time also the results were graphed properly on semilogarithmic paper so that the student can see at a glance when death rates get back to normal and can easily compare the death rate after an operation with that of the normal population of corresponding age (Fig 8)

In the past investigators have failed to take into account the fact that if at operation they had removed let us say the appendix rather

cases the differential diagnosis is not so important, because the patient should be operated on anyway, something must be done to relieve the pyloric obstruction and the decision as to what should be done can be made at the operating table

One of the roentgenologist's greatest difficulties is to differentiate carcinoma from chronic ulcerative gastritis An expert is likely to recognize gastric syphilis when he sees it, and usually he can recognize a benign tumor or an extrinsic lesion pressing on the stomach He may be puzzled at times by a peculiar conical appearance of the pars pylorica (Fig 7) due perhaps to spasm associated with a small gastric ulcer near the pylorus or to subacute cholecystitis

The roentgenologist usually can tell whether a growth is resectable, and the statistics of Walters Gray and Priestley show that, when an expert in this line warns the surgeon not to explore he had better decline to operate Only rarely, then will he be able to remove the growth, and if he does it probably will come back

Now that a few surgeons have perfected the technic of removing through the thorax the upper half of the stomach or even the whole organ together with the lower end of the esophagus, a few patients can be sent for exploration who would have been rejected a few years ago

As already pointed out in the section on gastritis, an expert roentgenologist usually is right in his diagnosis but there are a few cases in which he must remain uncertain, if only because the expert surgeon is puzzled when he has the lesion in his hand Comfort and Butsch (1938) reported some cases in which the surgeon, on exploring decided that the stomach was normal, but a few months later it was found to be full of carcinoma Helpful sometimes is the rule that ulcers on the greater curvature are nearly always malignant

When it appears that the radical removal of the growth is impossible, the next question is, should a gastro enterostomy be done? Again, the roentgenologist can help in making the decision He may report that the growth is so high in the stomach that there is no obstruction and hence no need for a palliative operation, or he may show that the lesion is so extensive that there is no healthy tissue left in which a stoma can be made

Gastroscopy —In a large number of cases today the gastroscopist can help in deciding whether a questionable lesion is benign or malignant, but he again can be wrong often His problems and his percentage of accurate diagnoses have been discussed already in the section on Gastritis Sometimes he can tell that the bottom of an ulcer is dirty looking,

cancer, who had only a palliative operation, were alive 5 years later and 0 7 per cent of those patients on whom only exploration had been performed were alive Apparently in an occasional case the cells of the body and those of a carcinoma fight each other to a stalemate which lasts for years and thus explains why an occasional patient who is treated by a quack stays well

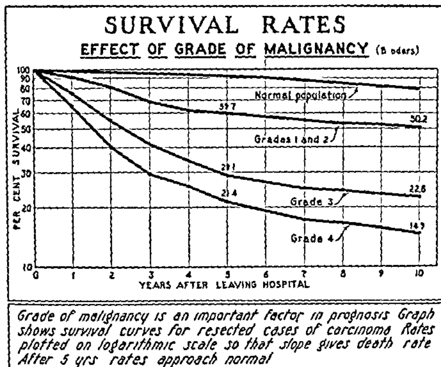


Fig 9 Survival rates of patients who had undergone gastrectomy for carcinoma of the stomach The patients were classified by grade of malignancy of the lesion (From Walters, Waltman Gray H K and Priestley J T., quoted in legend of Fig 8

That a long duration of symptoms does not necessarily rule out the possibility of a cure was shown by the fact that in the cases of 1 127 patients those whose symptoms had been present for 3 or 4 years had a survival rate 5 years after operation of 39 per cent while those whose period of illness was less than 3 months had a survival rate of 5 years after operation of only 21 per cent The reason for this apparent paradox is

than a carcinoma from 100 persons with an age averaging around 55 years and had had no operative deaths at the end of 5 years they would have had only 9 patients left they would have lost 8 simply because of the normal death rate for that age Because surgeons did not think to adjust their death rates for this normal disappearance of some of their

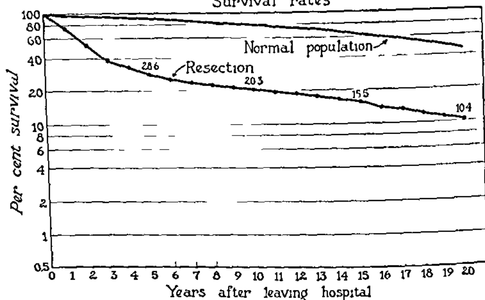


Fig 8 Survival rates of patients who had undergone gastrectomy for carcinoma of the stomach (From Walters Waltman Gray H K and Priestley J T Carcinoma and Other Malignant Lesions of the Stomach W B Saunders Company Philadelphia 1942

patients they turned out cancer statistics that were unnecessarily discouraging

One of the facts, which emerges strikingly from the big study of Walters and his associates, was the great prognostic value of the degree of malignancy of the lesion as determined by the pathologist and expressed on Broders' scale of 1 2, 3 and 4 In Fig 9, taken from the book of Walters Gray and Priestley it will be seen that at the end of 5 years, of the persons from whom a carcinoma graded 1 or 2 had been removed and who had recovered from the operation, 60 per cent were alive, 29 per cent of those whose tumor was graded 3 were alive, but only 21 per cent of those whose tumor was graded 4 had survived

Curious is the fact that 1 2 per cent of the patients with proved

Treatment

Obviously the only worth while treatment for cancer of the stomach is the early and complete surgical removal of the growth (Fig 10) When this operation cannot be carried out, and the presence of pyloric



Fig 10 The roentgenological picture seen after a posterior Polya type of partial gastrectomy with the anastomosis free

obstruction means that the patient is likely to die of starvation it may be advisable to perform gastroenterostomy granting that there is enough normal stomach left for the making of the anastomosis Not infrequently the performance of gastroenterostomy seems hardly desirable or worth while because it adds only two or three months to the patient's life

that those, who could go a long time before being forced to operation, probably had a tumor with a low degree of malignancy

Clinicians have long felt particularly hopeless about cancer of the stomach in young persons but the data published by Walters and his associates show that this attitude is not entirely justified In the case of patients less than 40 years of age the 5 years survival rate adjusted for noncancer deaths was 27 per cent while for oldsters from 60 to 70 years of age it was 35 per cent Obviously the old clinical hunch was correct but the difference is not large enough to warrant any feelings of despair, and still a man less than 40 years of age has one chance in four to recover

All pessimists should note also that 29 per cent of the persons, who had a gastric carcinoma removed and who recovered from the operation, were alive 5 years later Of those, who at the time of exploration had no visible metastasis or extension 46 per cent were alive 5 years later, and as already noted of those, who had a tumor of malignancy graded 1 or 2 60 per cent were alive 5 years later Doubtless these figures could have been greatly improved if only more patients with gastric cancer had gone to a good physician a few days after their symptoms appeared, and if only the physician had been keenly alive to the danger of treating medically anyone with a short history of indigestion and any type of deformity in the stomach As already noted, the sad fact is that even today 51 per cent of the patients, who begin to have symptoms of gastric cancer, are treated medically for more than a year, and largely as a result of this delay in only 57 per cent of the cases is exploration advisable In only 44 per cent of the cases, in which operation is performed is the lesion so small that it can be removed with some hope of success

Some patients and some physicians today still put off operation because of the fear of the immediate mortality of resection There can be no question that even in the hands of the ablest gastric surgeons available the mortality rate is considerable, but everyone should remember that without operation it is 98 per cent hence the patient with carcinoma has little choice as to treatment Actually in the Mayo Clinic series of cases the hospital mortality rate following resection for gastric carcinoma ranged from around 5 per cent for patients in the thirties to -4 per cent for patients in the seventies What is hopeful is that today with the increasing skill of surgeons and the increasing use of drugs, which often cure pneumonia and peritonitis, this mortality rate is coming down

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and these are not likely to be months of health or happiness which can give the patient any pleasure or his relatives any comfort

If operation appears hopeless, or if it is refused, then the mainstay must be a soft diet with sedatives If severe or troublous pain comes, and especially if the patient cannot sleep because of this pain, opiates should be given The best of these, for some persons at least, is dilaudid in doses of 1/16 grain (4 mgm) several times a day Members of the family sometimes will protest against the use of opiates, fearing that a habit will be formed or that life will be shortened, but they are wrong and they can be assured that life will be lengthened, if suffering can be avoided Furthermore the patient is not likely to live long enough to contract a habit I have seen patients, bedridden because of severe pain, get up and go about their business again, when given the rest and sleep that come with opiates Other sedative drugs of the barbiturate type are helpful if sleep is hard to get, and their quieting effect may cut down on the amount of dilaudid or morphine needed

The adherence to a liquid or soft diet may cut down a good deal on the gastric distress Treatment with roentgen rays is hardly advisable, it may upset the patient a great deal and it is not likely to do much good

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Benign Tumors of the Stomach

According to Eusterman and Senty only 1.3 per cent of all the many gastric tumors they studied proved at operation to be benign. Doubtless many small benign tumors are missed clinically or during the roentgenological examination. Kieniets who examined the stomach at [illegible]00 consecutive necropsies discovered 34 leiomyomas. Rigler and Ericksen among 39 gastric tumors diagnosed roentgenologically found 11 per cent that were benign.

Types of Benign Tumors

Benign gastric tumors may originate in either epithelial or connective tissue. Among the epithelial tumors most are adenomatous polyps and the rest are adenomas and papillomas. Among the connective tissue tumors one finds leiomyomas, fibromyomas, adenomyomas and myxofibromas. In addition there are a few hemangiomas, fibromas, neurofibromas, dermoid cysts and lipomas.

Heeks and Gibb (1942) reviewed the literature on the rare type of gastric polyposis (Fig. 11) in which there are scores of small tumors in the stomach. This condition resembles that in the colon. Some of the gastric polyps contain cancer cells, usually of low malignancy.

Symptoms

Most of the small or benign tumors, if located in the midregion of the stomach, are not likely to cause symptoms of any kind. Occasionally there will be bleeding because of ulceration of the mucosa over the tumor.

Pedunculated Tumors Prolapsing Through the Pyloric Ring.—Rarely one will see a pedunculated polyp which prolapses through the pyloric ring and causes perhaps nausea, pain or slight obstruction. These lesions were described in 19[illegible]6 by Eliason, Pendergrass and Wright. Operation usually is advisable because some of these polypoid lesions become cancerous. In some cases nausea or hemorrhage forces the patient to operation.

Roentgenological Diagnosis

In 1924 and 1927 Moore showed that most of the benign tumors produce an oval or circular filling defect which is likely to be situated

Linitis Plastica

Linitis plastica or "leather-bottle stomach" is a name given by Brinton years ago to a disease of the stomach, which causes its walls to contract and become tough and leathery Today the name might perhaps be discarded because the modern pathologist practically always can find cancer cells tucked away here and there in the mass of connective tissue In some cases the stomach is almost a replica made of cancer cells A better term is "scirrhous carcinoma of the stomach"

Sarcoma of the Stomach

Less than 1 per cent of gastric tumors are sarcomas Lwing divided them into three groups (1) spindle-celled myosarcomas, (2) lymphosarcomas and (3) miscellaneous round celled and alveolar types They form solid or cystic growths often large which begin in the submucosa or muscle and finally project sometimes with a pedicle either into the lumen of the stomach or out under the peritoneum Since they do not tend to invade the mucous membrane they ulcerate late

The symptoms and signs are practically those of carcinoma The commonest complaints are indigestion pain tumor bleeding weakness and vomiting The treatment is the same as that for carcinoma Balfour and McCann reported that of 38 patients from whom a gastric sarcoma was removed 12 were living when last heard from and 26 were dead The average postoperative duration of life in those who died was 11 months

Lymphosarcomas sometimes respond beautifully to roentgen therapy, and probably it is well to use this type of treatment after operative removal of any sarcoma

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Treatment

If there is doubt about the nature of an apparently benign tumor or if it is causing hemorrhage, the patient should be operated on The tumor usually can be removed through an opening in the gastric wall



Fig 12 Benign tumor of the greater curvature of the stomach

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somewhere in the middle of the barium shadow, not touching either the greater or the lesser curvature Fig 12 shows a benign tumor of the greater curvature An aphorism worth remembering is that 'half of the benign tumors of the stomach are malignant"



Fig 11 Polyposis of the stomach

Gastroscopy

The gastroscopist is now very helpful in enabling the clinician and the roentgenologist to be sure that they are dealing with a benign tumor He can help in differentiating benign and malignant polyps

the roentgenologist will see a long narrow tube hanging from a pouch at the cardia There is little or no longitudinal contraction of the stomach A striking feature may be the absence of a palpable mass corresponding to the large defect Scirrhous cancer may give a picture which somewhat resembles that of gastric syphilis but the filling defect is likely to be nearer one curvature than the other and to be tortuous and uneven in outline furthermore a mass probably will be felt

The average age of the patients is 36 years and they generally have had syphilis for 10 years or more The character of the symptoms depends naturally on the location of the lesion the degree of obstruction at the pylorus and the extent of the destruction ulceration and contraction of the stomach

In two thirds of the 93 cases reported by Eusterman in 1951 the main complaint was that of epigastric pain or discomfort immediately after eating This was relieved somewhat when the food was made more liquid In every case the symptoms had been getting progressively worse so that by the time the patients arrived most of them were more or less emaciated and were living on liquids The impression to be gained from the history was that the *stomach must be shrunken Often there was* vomiting without nausea The appetite usually was unchanged In 15 per cent of the cases the symptoms were *mild and suggestive of the* presence of cancer Occasionally the distress was relieved by the taking of food or alkalies In 23 per cent the symptoms were like those of ulcer Only 5 of the 93 patients gave a history of bleeding In [illegible]4 per cent there was some pyloric obstruction A palpable mass was present in [illegible]0 per cent Achlorhydria was present in 85 per cent and in a number of the cases in which histamine was tried there was no secretion The Wassermann reaction was negative in 7 cases Twenty seven per cent of these patients with gastric syphilis showed other signs of the syphilis

Thirty seven per cent were cured later and 4[illegible] per cent greatly improved Twenty eight of the 93 were operated on and in 14 the lesion was excised

Treatment of Gastric Syphilis

If the lesion in the stomach looks much like a carcinoma it is best to go ahead and resect it even if the tests for syphilis are positive It may be too dangerous to wait for the results of treatment with drugs Before the operation the syphilologist may want to give a small amount of treatment by way of preparation After such treatment is started one of the

Gastric Syphilis

Gastric syphilis is a rare disease. At the Mayo Clinic 40 cases were collected during a period in which 6,000 cases of ulcer and gastric cancer were seen. McNeil (1917) found that only 8 per cent of 1,200 syphilitics complained of indigestion and in only 2 of these cases was there definite gastric syphilis. In a series of 600 syphilitics White (1917) found 7.3 per cent with prominent gastric symptoms, a figure which agrees well with that of McNeil. Naturally not all of the gastrointestinal troubles which appear in men and women with a positive Wassermann reaction can be ascribed to syphilis of the stomach.

The lesion generally is a tertiary one and not infrequently is due to a gumma which starts generally in the submucosa and later breaks down, producing ulceration with fibrosis, contraction and partial healing. Microscopical examination of the lesion should show endarteritis and periarteritis and the usual picture of gummatous degeneration. There is a syphilitic type of gastritis. In some cases one may see through the gastroscope large shallow and perhaps irregularly shaped lesions involving an area of the stomach in which the wall seems to be stiff and infiltrated and perhaps a little nodular. The floor of the ulcer may be dirty, and there may be some whitish areas about it. There may be other small ulcers adjacent to the main big one, and scars from the healing of previous ulcers may be noted.

An ulcerating lesion associated with achlorhydria and not cancerous in appearance should make one think of gastric syphilis, especially if the tests for syphilis are positive. Even under these circumstances, however, the lesion still may be carcinomatous. It must be remembered that in the stomach carcinoma is immensely more common than is syphilis.

According to Moore and Aurelius the most characteristic roentgenological sign of gastric syphilis is a filling defect which reduces the lumen of the stomach to a narrow tube situated midway between the two curvatures. The channel practically always is straight with fairly smooth margins. Sometimes there will be a few small pockets here and there. The rugae are obliterated, and the wall of the stomach is less pliable than it should be. In three fourths of the cases the stenosis is in the lower end of the stomach. The barium shadow often will have a spicular form with the point directed toward the pylorus. In a fourth of the cases the hour glass contraction is in the middle region of the stomach. The channel then is long, narrow and centrally placed. In less than a tenth of the cases almost the entire stomach is affected, and

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Hair Balls and Bezoars

Gastric tumors are seen occasionally in which the mass turns out to be a large hair ball or bezoar or an accumulation of hardware swallowed by the patient Naturally these things are seen commonly in insane asylums An interesting bezoar is the one produced by eating at one meal a number of persimmons The diagnosis of hair ball or bezoar usually is made with the roentgen rays, and the treatment consists of surgical removal of the mass



Fig 13 Diverticulum of the stomach in the usual place near the cardia also one in the duodenum and a duodenal ulcer

Diverticula of the Stomach

Gastric diverticula are rare Rivers Stevens and Kirklin found 4 during the course of 3,662 necropsies Most of them probably do not produce symptoms and are discovered only accidentally during roent

genological study Most of them are on the lesser curvature just below the cardia (Fig 13) a few are on the top of the stomach

The differentiation between a diverticulum and a deeply penetrating peptic ulcer is not always easy Fortunately for the diagnostician ulcers rarely are seen just below the cardia, and usually the neck of the pouch can be seen to be much narrower than one would expect it to be, if it had been formed by ulceration

Treatment

If an experienced gastroenterologist concludes that the symptoms complained of by the patient are not due to the diverticulum it had better be left alone Probably only rarely is it justifiable to remove it

Acute Dilatation of Stomach

This is a condition which in the old days used to cause death after operations Fortunately today perhaps partly because operations are not preceded by violent purgation probably because they are done usually with greater skill and speed and hence with less shock and partly because at the least sign of postoperative gastric stasis or shock a stomach tube is put down the syndrome is seen but seldom

The phenomenon has been observed after injuries to the head or to the spine and it is said to occur sometimes after the application of a large body cast Unless the condition is discovered promptly and relieved by the passage of a large stomach tube, the patient is likely to die

The condition may announce itself only through its harmful effects on the circulation and the nervous system Dr W J Mayo used to say that just as the medical resident carries a stethoscope hanging from his neck the surgical resident should go around similarly draped with a stomach tube

Some writers have reported that the condition sometimes straightens out if the patient is put on his abdomen With the passage of a tube and the emptying of the stomach the patient usually recovers in a few minutes

Hypertrophy of the Pyloric Muscle in Adults

Occasionally one will see a patient with signs of pyloric obstruction and considerable hypertrophy of the muscle at the pyloric ring In a

few cases this appears to be a remnant of a congenital pyloric stenosis In other cases it is probably a separate disease

Diagnosis

Sometimes the roentgenologic picture is typical the shadow of the pyloric muscle projecting into the cavity of the first portion of the duodenum A similar picture may be produced by a redundancy of the mucous membrane of the pars pylorica

Treatment

If there should be definite pyloric obstruction the treatment should be either gastroenterostomy pyloroplasty or partial gastrectomy In at least one case watched over several years, the hypertrophy finally dis appeared In some cases in which pylorectomy was done, the clinical result was not satisfactory and the pain and discomfort remained

September 1 1948

CHAPTER II-A

GASTROSCOPY

By EDWARD B BENEDICT

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INTRODUCTION

The first man ever to attempt gastroscopy was Kussmaul[1] who in 1868 passed a partially flexible gastroscope on a professional sword swallower Since at that time the electric light had not been invented Kussmaul depended on an external source of light a lamp devised by Désormaux Due to the fact that the lighting system was entirely inadequate for proper illumination of the interior of the stomach no satisfactory results were obtained Kussmaul later abandoned the partially flexible tube and used a straight metal tube with a flexible obturator *Therefore although he was unable to study the gastric mucosa he did* demonstrate the important anatomical fact that a straight rigid instrument could be introduced through the mouth into the stomach

In 1881 Mikulicz[2] made further attempts using an elbowed gastroscope With this instrument he was able to see the interior of the stomach but the difficulties and dangers of the method were so great that he abandoned it Others who did notable work in developing gastroscopy were Rosenheim (1895)[3] Kelling (1897)[4] and Kuttner (1897)[5] In 1907 Chevalier Jackson[6] began the use of straight rigid open tube gastroscopes and made a few observations regarding the gastric mucosa in inflammatory and neoplastic conditions There were however so many areas in the

stomach which could not be examined by the open tube method and so many difficulties and dangers in the passage of a rigid tube for purely diagnostic purposes that his work was confined largely to removal of foreign bodies from the stomach. In 1911 important contributions were made by Elsner, Sussmann[8] and Hoffmann[9].

In 1920 Schindler[10] first became interested in gastroscopy and used a rigid lens system gastroscope for many years. Because of occasional accidents he was not satisfied with the instrument and in collaboration with Wolf, an optical physicist, finally developed in 1932 the Wolf Schindler flexible gastroscope[11]. Modern gastroscopy dates entirely from the development of this instrument. Benedict[12] was the first to use the flexible gastroscope in the United States. Arafa[13], Edwards[14] and Rodgers[15] introduced the method in England. Gastroscopy has now become a well established method of examining the stomach and is in daily use in all the large cities of the United States. The development of gastroscopy in this country was stimulated greatly by Schindler's arrival here in 1935.

Technique

The present instrument is rigid in its proximal portion and flexible in its distal portion. The proximal rigidity enables a proper guiding and turning of the instrument by the operator, and the flexibility of the distal portion permits ease and safety of introduction. The optical system consists of many convex lenses with a prism at the distal end so that the view is at right angles to the axis of the instrument. Illumination is effected by an electric light at the distal end of the instrument. While this light is entirely satisfactory for observation, it is insufficient for good photography. At the present time the instrument can be used only for observation and not for operating, but attempts have been made already to widen the field of gastroscopy by a biopsy attachment (Kenamore[16]).

Gastroscopy is a comparatively simple procedure which may be performed in the office or in the Out Patient Department. It should not be considered an operation as it hardly amounts to more than passing a large stomach tube. Some patients have even remarked that they prefer gastroscopy to gastric lavage with the small nasal tube. Most physicians seeing gastroscopy for the first time have been amazed at the simplicity of the procedure. It is performed under local anesthesia. The stomach should of course be empty, but lavage is necessary only in cases of pyloric obstruction. Preliminary medication consists of morphine gr 1/6 (10 mgm.) with atropine, gr 1/150 (0.375 mgm.) given subcutaneously

shortly before the instrument is passed Nembutal may be used in addition if deemed advisable but when the procedure is done in the office or Out Patient Department it is best to use as little sedation as possible Local anesthesia of the throat is obtained by a gargle of 2 per cent pantocaine

The patient lies on his left side with the head supported on small pillows or in the hands of a trained assistant The writer has found the former method entirely satisfactory in fact the patient usually relaxes better with pillows than with the head held by the average hospital nurse or orderly If an expert assistant is present however head holding may be an advantage The patient lies quite passively no swallowing motion being required The passage of the gastroscope is done entirely by the operator who introduces the fingers of the left hand to the base of the tongue and gently insinuates the flexible finger tip of the gastroscope into the posterior pharynx past the cricopharyngeus and into the esophagus Although some writers have advocated the rapid passage of the gastroscope through the esophagus in order to avoid spasm it has seemed safer to the writer to pass it slowly

The question is often asked Is gastroscopy a safe method of examination? In order to answer this Schindler[17] recently has published the results of a questionnaire regarding fatalities in gastroscopies Over 22 000 gastroscopies were reported with one fatality This patient had also had bronchoscopy thoracoscopy artificial pneumothorax and sternal puncture before the gastroscopic examination Autopsy showed a diffuse carcinomatosis of the left lung and pleura with a small perforation of the esophagus and a large abscess in the posterior mediastinum One other fatality has occurred since these results were published This occurred in a patient 63 years of age who had pernicious anemia with very marked atrophy of the gastric mucosa The mucosa was so thin that a perforation occurred and in spite of the fact that the stomach wall was repaired immediately by careful suture the patient developed subphrenic and liver abscesses and finally died six months following gastroscopy The mortality from the examination may therefore be said to be 0 009 per cent Eight other perforations of the stomach have been reported and one perforation of the jejunum in a resected stomach All of these patients recovered The procedure may therefore be considered comparatively safe

The medical profession has been wondering who should perform gastroscopy internists surgeons laryngologists or gastroenterologists The technique of passing the instrument is fairly simple and no special training in surgery or laryngology is required Since the correct interpretation of gastroscopic findings is however very difficult a special knowledge of

and interest in the stomach is of primary importance Therefore gastroscopy should be performed by those primarily interested in gastroenterology Much harm may result from reliance upon the observations of a poorly trained gastroscopist or one who makes only occasional examinations The procedure will of course be done most commonly in large hospitals where collaboration may be had with all branches of the profession especially gastroenterologists roentgenologists internists and surgeons Gastroscopy in no way supplants or competes with other methods of examination it is an important addition to our diagnostic methods in diseases of the stomach

Indications and Contraindications

As recently outlined by Benedict[18] the indications for gastroscopy are as follows (1) gastritis or suspected gastritis (2) unexplained gastric hemorrhage (3) so called gastric neurosis (4) where x ray examination is negative but gastrointestinal symptoms persist (5) where x ray examination is inconclusive (6) gastric ulcer (7) duodenal ulcer (8) to help differentiate benign from malignant lesions (9) to help determine the nature extent and operability of benign and malignant gastric tumors (10) to study the gastric mucosa in various diseases especially pernicious anemia and other deficiency states to follow the effect of therapy in such cases and to diagnose the early neoplastic change known to be more frequent in an atrophic gastric mucosa In other words gastroscopy is an extremely important method of examining the stomach wherever gastric disease is known or suspected It has been truly said that gastroscopy should bear the same relation to gastroenterology that cystoscopy bears to urology

There are relatively few contraindications to the passage of the gastroscope Esophageal obstruction is the only absolute contraindication Aortic aneurysm probably should be considered a contraindication In order to exclude esophageal obstruction it is the policy of the author always to have x ray examination of the esophagus before gastroscopy Among the relative contraindications which should be mentioned are esophageal varices esophageal diverticulum cardiac decompensation cervical arthritis and marked debility Extreme kyphosis or psychoneurosis also may be contraindications Occasionally patients are so uncooperative that gastroscopy may be very difficult or unwise

It should be borne in mind also that gastroscopy like most other procedures has certain limitations In addition to the above absolute or relative contraindications there are some difficulties of examination and

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It should be borne in mind also that gastroscopy like most other procedures has certain limitations In addition to the above absolute or relative contraindications there are some difficulties of examination and

interpretation Some stomachs as well as some patients are much easier to examine than others In the J shaped stomach it may be hard to visualize the pylorus and the lesser curvature near the pylorus due to angulation of the stomach Because of the fact that the objective lens is at right angles to the axis of the instrument it may be difficult to inspect the region along the greater curvature where the tip of the gastroscope impinges upon the gastric wall Another region which sometimes is hard to see is the posterior wall near the cardiac orifice for at this point the gastroscope may be too close to the mucosa to allow proper observation Areas high up in the fundus of the stomach adjacent to the esophagus may be difficult to visualize By proper manipulation of the instrument and the patient however and by careful observation during various phases of respiration and peristalsis many of these so called blind areas can be eliminated

The correct interpretation of gastroscopic findings may be extremely difficult The physician who does only an occasional gastroscopy cannot be relied upon for proper interpretation Even an experienced observer may have great difficulty in differentiating for example a benign from a malignant ulcer or severe hypertrophic gastritis from a diffuse infiltrating carcinoma In such doubtful cases the clinician naturally must consider the case as a whole and base his diagnosis not only upon gastroscopy and x ray examination but also upon the history physical examination and laboratory findings Furthermore the gastroscopist frequently will see minor pathological changes in the stomach mucosa which hardly can be considered the cause of symptoms Having made due allowance for all the limitations of the method one cannot escape the conclusion that gastroscopy has given us very important information regarding the gastric mucosa which has been impossible to obtain by any other method of examination

Normal Stomach

The normal gastric mucosa presents a brilliant orange red appearance (Figs 1–5) The color is fairly uniform throughout the stomach The walls are smooth the rugæ are of moderate size small or absent along the lesser curvature and anterior wall larger and somewhat more tortuous along the greater curvature and posterior wall The size of the folds varies considerably with the amount of air introduced into the stomach the rugæ naturally tending to disappear almost entirely when the stomach is over inflated The color of the stomach may change also and become somewhat more pale with greater distention In the normal stomach the

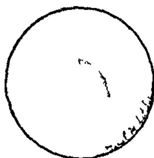


Fig 1



Fig 2

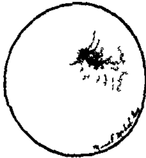


Fig 3

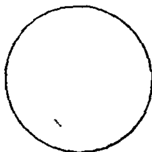


Fig 4

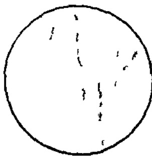


Fig 5



Fig 6



Fig 7

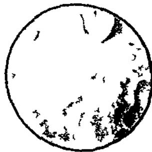


Fig 8



Fig 9

Fig 1 Norm l angulu and antrum with pylorus in the di tance normal smooth mucosa with characteristic orange red col r

Fig 2 Normal stomach sho ing peristaltic wave progressing toward pylorus the pylorus is een slightly open in the centre background

Fig 3 Normal stomach showing complete closure of the pylorus

Fig 4 Normal stomach anterior wall and lesser curvature normal smooth orange red mucosa with few small parallel rugae

Fig 5 Normal stomach greater curvature the mucosa is smooth and of normal color but the rugae are larger and slightly more tortuous than in Fig 4

Fig 6 Superficial gastritis note particularly the reddening and edema of the mucosa with adherent exudate

Fig 7 Hypertrophic gastritis note the marked verrucous cobblestone appearance of the muco a proximal to the angulus the antrum is smooth and normal

Fig 8 Hypertrophic ga tritis very large bulbous tortuous rugae with verrucous formation

Fig 9 Hypertrophic gastritis note the two superficial ero ions this patient had suffered uch severe hemorrhage from gastritis alone that re ection was required the pathological report of ga triti witho t ulcer confirmed the gastroscopic findings

other times irregular circumscribed red patches varying in size or extent from half an inch to an inch and a half in circumference are found on the internal coat These appear to be the effect of congestion in the minute blood vessel of the stomach There are also seen at times small aphthous crusts in connection with these red patches Abrasions of the lining membrane like the rolling up of the mucous coat into small shred or strings leaving the papillæ bare for an indefinite space is not an uncommon appearance

Beaumont also observed erythema aphthous patches exuding of blood ropy mucus and mucopurulent matter all of which appearances now are confirmed repeatedly by gastroscopy

Acute gastritis is seen most commonly following an alcoholic debauch These patients are as a rule too ill to submit to gastroscopy but gas troscopic observations have been made showing very marked reddening and edema of the mucosa throughout the stomach Submucosal hem orrhage may occur and may be very severe In fact death has been reported to have occurred from very severe alcoholic gastritis with hemor rhage (Benedict [1]) This has been confirmed at autopsy where no ulcer was found but the gastric mucosa showed chronic gastritis with multiple erosions and hemorrhage Indiscretions in eating as well as in drinking may lead to acute gastritis which usually heals up readily when the cause has been removed When however the overindulgence in eating and drinking has been long continued chronic gastritis may develop Another form of acute gastritis which should be mentioned is the acute phlegmon ous type which dissects along the layers of the stomach wall with pus formation In this condition there may be high fever severe pain and vomiting with prostration When such symptoms are present gastroscopy is contraindicated

Chronic gastritis from the gastroscopic standpoint is divided into super ficial hypertrophic atrophic and postoperative types Although this classification forms a convenient and useful basis for discussion it is not always possible to adhere closely to it for superficial changes are found frequently in hypertrophic and postoperative gastritis Certain stomachs may even show areas of atrophy while other areas show hypertrophic changes Many ways of classifying gastritis have been suggested no one of which is altogether satisfactory Until more is learned about gastritis and the relationship between the gastroscopic and pathological findings the above classification is convenient and useful

Pathological evidence of chronic gastritis is obtained largely from stomachs which have been resected for ulcer or neoplasm where there is usually an associated gastritis In such cases the gastroscopic findings are confirmed by microscopic study In a few cases of chronic gastritis

mucosa is of sufficient thickness so that no blood vessels are seen shining through it. The mucosa throughout is normally smooth, glistening, moist and exhibits many small high lights. Varying amounts of mucus may be present appearing as small bubbles and in large amounts may interfere considerably with accurate observation.

During gastroscopic examination the stomach usually is found to be in constant motion not only from transmitted pulsations and respiratory motion but also from its own peristaltic activity. The experienced observer finds no difficulty from the transmitted pulsations and soon learns that advantage may be taken of deep inspiration or forced expiration and of peristaltic movements to improve his inspection of all parts of the stomach. The peristaltic waves very seldom are seen proximal to the angulus but frequently are well observed passing down the antrum to the pylorus. The pylorus itself may be visualized in 80 to 90 per cent. of the cases.

Gastritis

According to some authorities gastritis is the commonest disease of the stomach. Certainly it is a very common condition. It not only occurs alone as a pathological entity but also occurs very frequently in association with gastric ulcer, duodenal ulcer and carcinoma. Although gastroscopic proof is lacking, there is clinical and pathological evidence that gastritis occurs as an acute process in many infectious diseases (Beaumont[19], Faber[20]).

Beaumont was the first to study the gastric mucosa under such conditions. He made direct observations on the stomach of his servant Alexis St. Martin, who had an open gastric fistula. Beaumont writes as follows:

> In febrile diathesis, or predisposition from whatever cause — obstructed perspiration, undue excitement by stimulating liquors, overloading the stomach with food — fear, anger, or whatever depresses or disturbs the nervous system — the villous coat becomes sometimes red and dry, at other times pale and moist, and loses its smooth and healthy appearance; the secretions become vitiated, greatly diminished or entirely suppressed; the mucous coat scarcely perceptible; the follicles flat and flaccid, with secretions insufficient to protect the vascular and nervous papillae from irritation.
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> "There are sometimes found on the internal coat of the stomach eruptions or deep red pimples, not numerous, but distributed here and there upon the villous membrane, rising above the surface of the mucous coat. These are at first sharp pointed and red, but frequently become filled with white purulent matter. At

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> There are sometimes found on the internal coat of the stomach eruptions or deep red pimples not numerous but distributed here and there upon the villous membrane rising above the surface of the mucous coat These are at first sharp pointed and red but frequently become filled with white purulent matter At

cases alkaline powders belladonna and colloidal aluminum hydroxide Liver therapy may be of benefit and has been administered in certain cases on the theory that it has a specific action on the gastric mucosa as has been demonstrated in pernicious anemia (Jones Benedict and Hampton) Superficial gastritis usually runs a short course most patients reporting marked improvement or complete absence of symptoms at the end of three months When gastroscopy is repeated at this time the mucosa will show a complete return to normal

In *hypertrophic gastritis* the characteristic gastroscopic picture is the verrucous appearance of the gastric mucosa (Fig 7) This will vary from a granular or wart like formation to a real cobblestone pattern The rugae may be beaded or segmented like a caterpillar and sometimes appear bulbous and tortuous The hypertrophy of the rugæ interpreted by roentgenologists as hypertrophic gastritis is seldom seen by gastroscopy though a diagnosis of gastritis by an experienced radiologist usually is of significance and is an indication for gastroscopic examination X ray examination is positive in only 20 per cent of the cases of hypertrophic gastritis Only by gastroscopy is it possible to determine the type extent and severity of the gastritis and the presence or absence of erosions or superficial ulcerations (Figs 9 and 10) Active bleeding seen at gastroscopy occurs in about one quarter of the cases In the acute stage of hypertrophic gastritis increased reddening of the mucosa is characteristic During the quiescent stage the mucosa may appear dull but the verrucous formation usually persists

The symptomatology of chronic hypertrophic gastritis is variable Most patients complain of gas and epigastric distress Nausea and vomiting occur in about one third of the cases Anorexia heartburn and sour eructations are infrequent About half the patients give a history of some degree of bleeding Massive even fatal hemorrhage may occur

The treatment of hypertrophic gastritis as in superficial gastritis still is empirical and largely symptomatic All patients suffering from hypertrophic gastritis should be placed on a bland diet with frequent feedings Relief may follow the use of alkaline powders and belladonna The use of liver concentrates may be tried and iron and vitamin preparations may be used with benefit when proper indications exist In our experience most patients have been relieved entirely or very much improved on this form of therapy

Atrophic gastritis generally is regarded as the end stage of mucosal atrophy Since it is hardly an inflammatory process either as seen gastroscopically or as studied histologically some other nomenclature might be better (Jones[4]) Complete atrophy of the gastric mucosa (Fig 11)

without other pathology but with intractable symptoms or hemorrhage resection has been carried out In these cases the gastroscopic findings have been confirmed on microscopical section Superficial gastritis is recognized pathologically by cellular infiltration and in some cases by capillary enlargement and hemorrhage Hypertrophic gastritis is distinguished histologically by proliferation of the mucosa and cellular infiltration Atrophy of the gastric mucosa often spoken of as atrophic gastritis is considered by many to be the end stage of chronic gastritis In this condition the whole mucosa is thin and atrophic with an absence of gland formation

The etiology of chronic gastritis is not known but there is little doubt that indiscretions in diet are of great importance Overindulgence in alcohol spicy or highly seasoned foods predisposes to gastritis Excessive use of tobacco may be a factor Foci of infection in the teeth tonsils gall bladder or elsewhere may be of significance, though it is impossible to find any specific bacterial agent

Superficial gastritis is characterized gastroscopically by reddening and edema of the gastric mucosa with the formation of exudate (Fig 6) According to some authorities all three of these criteria must be present but in the opinion of the writer exudate is encountered rather infrequently and edema may or may not be demonstrable All cases do however show an increased reddening of the mucosa This reddening occurs typically on the crests of the rugae but may appear elsewhere as irregular blotchy areas of intense hyperemia The mucosa may present a swollen glistening appearance The presence of exudate in the stomach sometimes is difficult to determine as it may be confused with other gastric secretions When exudate occurs frequently it is seen adherent to the gastric mucosa or lying in the valleys between the folds Superficial erosions and pigment spots are not uncommon Some degree of hemorrhage occurs in about one third of the cases Gastric analysis and x ray examination will disclose no variation from the normal

Patients suffering from superficial gastritis usually fall into the middle decades of life Men are more susceptible than women but the disease occurs in both sexes The most frequent symptom is gas Epigastric distress, nausea and vomiting are common symptoms Anorexia and heartburn may occur Sour eructations and fulness are infrequent Abdominal pain usually epigastric is complained of by some patients but ordinarily is not severe Mild to moderate bleeding occurs in about one third of the cases

With regard to treatment most patients respond well to a 6-meal bland diet and the usual medical regimen for ulcer including in some



FIG 10

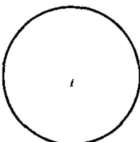


FIG 11



FIG 12



FIG 13



FIG 14



FIG 15



FIG 16



FIG 17



FIG 18

FIG 10 Hypertrophic gastritis with severe hemorrhage note the beading of the rugae and the hemorrhagic appearance throughout in this patient the mucosa was extremely friable and oozing of blood occurred from many areas

FIG 11 Gastric atrophy note the very pale thin mucosa with blood vessels shining through it atrophy is seen not only in pernicious anemia and other deficiency diseases but also without any recognizable deficiency disease

FIG 12 Return of gastric mucosa to normal after liver therapy same case as shown in Figure 11

FIG 13 Acute gastric ulcer with sharp bright red margin and clean base usually the diagnosis of gastric ulcer is made by x ray examination but superficial ulcers such as the one shown in this illustration not infrequently are overlooked by x ray

FIG 14 Small benign healing gastric ulcer on the edge of the angulus rugae are converging toward the ulcer note the sharp margins and clean gray base characteristic of a benign lesion

FIG 15 Malignant gastric ulcer note the irregular nodular margin with dirty brown base note also the hypertrophic gastritis associated with the ulcer

FIG 16 Large carcinoma of greater curvature diagnosis first made in this case by gastroscopy as the roentgenologist although he described a small oval filling defect of the antrum had difficulty in palpating this very high lesion

FIG 17 Foreign bodies in the stomach a prune stone and a plum stone diagnosis established by gastroscopy

FIG 18 Submucosal tumor as seen by gastroscopy gastroscopic diagnosis of neurofibroma or fibromyoma was made resection was performed and the diagnosis of neurofibroma confirmed histologically

absence of associated gastritis in duodenal, gastric and gastrojejunal ulcer

The diagnosis of *gastric ulcer* usually is made by x ray examination In certain cases however where the ulcer is superficial or roentgenological examination is difficult the gastroscopist may be the first to establish a positive diagnosis Such cases are rare but important More frequently gastroscopy is requested to confirm an x ray diagnosis in which case information may be gained regarding the gross appearance of the lesion A bright red margin means an acute ulcer (Fig 13) A clean gray shallow base with non inflamed margins indicates healing (Fig 14) A definitely nodular margin with a dirty irregular base indicates malignancy (Fig 15) In some borderline cases it may be impossible to differentiate benign from malignant ulcer by any means at our disposal Occasionally a large ulcer of questionable character may be demonstrated by x ray and gastroscopy may not only establish its benign or malignant character but may disclose also additional ulceration and give important information regarding the presence of gastritis and erosions The demonstration of multiple ulcers is important in itself but particularly so when the question of malignancy arises for multiple malignant ulcers in different parts of the stomach are extremely rare whereas multiple benign ulcers are not uncommon Sometimes unfortunately gastric ulcers demonstrated by x ray are not visible by gastroscopy This may be due to the blind areas in the stomach already mentioned or may be because of an uncooperative patient In general however it may be said that gastroscopic examination in gastric ulcer usually gives valuable information not obtainable by any other method

The direct visualization of the stomach in cases of *duodenal ulcer* is of importance chiefly in giving information regarding the presence or absence of gastritis Some gastritis usually is associated with duodenal ulcer Evidence is accumulating that the gastritis in some cases is of more importance than the ulcer not only as a cause of symptoms but also as a source of hemorrhage Occasionally a duodenal ulcer may be healing by x ray but symptomatically the patient may be getting worse In such a case gastroscopy may reveal a severe gastritis as the chief cause of the symptoms Not infrequently in cases of hematemesis or melena the clinician may be satisfied with an x ray diagnosis of duodenal deformity or healed duodenal ulcer to explain the bleeding In some such cases however it has been shown at autopsy that the bleeding occurred from the associated gastritis and not from the old inactive ulcer[30] A knowledge of the appearance of the gastric mucosa is therefore of importance in planning an operation for duodenal ulcer for the type of operation or the extent of resection may be influenced by the degree of gastritis present

Gastroscopic examination in *gastrojejunal ulcer* has proved of value

chiefly in confirming a diagnosis already suggested or established by x ray Unfortunately some ulcers in the jejunum may not be visible by gastroscopy as they may be too far from the stoma In other cases the stoma itself may be poorly visualized While gastroscopy cannot exclude gastrojejunal ulcer it may give other valuable information regarding gastritis with erosions and hemorrhage Direct inspection of a gastrojejunal ulcer gives evidence regarding its size base margins and surrounding mucosa which enables an evaluation of its activity The information obtained by gastroscopic examination of the postoperative stomach may be the determining factor in deciding whether to continue medical treatment or to resort to further surgery

TUMOR

Direct inspection of the gastric mucosa in cases of known or suspected gastric tumor has led to a more precise knowledge of the gross appearance and extent of the lesion Occasionally a diagnosis of gastric tumor will be established first by gastroscopy (Fig 16) sometimes a questionable lesion will be excluded or confirmed and always the nature and extent of the tumor will be studied carefully by direct inspection With increased knowledge regarding the gross appearance of the tumor and its classification according to the Borrmann typing Schindler[31] believes that a more reliable prognosis may become possible before surgical intervention and that in certain cases it will be possible to predict incurability without operation In the present state of our knowledge this concept seems rather far reaching but several factors are already at work to make it attainable I refer (1) to the greatly increased use of the gastroscope which should help to correlate the gross appearance of the lesion with its prognosis (macroscopic type) (2) to the use of gastroscopic biopsy forceps[16] which will give us data on the histology of the tumor (microscopic grade) and (3) to the use of the peritoneoscope (Ruddock[3] Benedict[33]) which saves exploratory laparotomy in advanced cases by positive biopsy from metastatic carcinoma in the liver and peritoneum

In the early diagnosis of *carcinoma* gastroscopy plays an important role for as already mentioned it is known that an atrophic gastric mucosa is fertile soil for the development of cancer and the only positive method of making a diagnosis of atrophy of the mucosa is by gastroscopy Atrophy of the mucosa is seen commonly in untreated pernicious anemia and in early or treated cases may or may not be present Having established the presence of atrophy by gastroscopic examination frequent study both by x ray and gastroscopy is indicated to detect at the earliest

also the great need for a more exact prognostic diagnosis in gastric neoplasm

Conclusions

Gastroscopy with the flexible gastroscope is a comparatively easy and safe method of examining the stomach It gives information regarding the gastric mucosa which is not obtainable by any other method The indications for gastroscopy are many and are outlined above Contraindications are few The value of the method is in direct proportion to the knowledge skill and experience of the observer The procedure is of particular value in the diagnosis of the commonest disease of the stomach namely chronic gastritis It has been shown by gastroscopy and confirmed pathologically that severe hemorrhage occurs from gastritis alone Gastroscopy is also of great value in the study of peptic ulcer benign and malignant tumor and in deficiency diseases With increasing use of the gastroscope and with improvements in the instrument gastroscopy will bear the same relationship to gastroenterology that cystoscopy bears to urology

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moment the possible development of neoplasm Gastric atrophy occurs also in the deficiency diseases namely sprue, scurvy pellagra and Plummer Vinson syndrome and here again the clinician should be on the alert to make this diagnosis and if cancer should develop, to detect it early by having frequent x ray and gastroscopic examinations Gastric atrophy although it may represent a deficiency state is seen also in the absence of any demonstrable deficiency disease According to Faber[20] atrophy represents the end stage of chronic gastritis Although many cases of chronic gastritis probably never go on to complete atrophy, a sufficient number of them probably do go on to atrophy to make the diagnosis of chronic gastritis of great importance not only in itself but also because of its relationship to cancer Hurst[34] and Konjetzny[35] have contended for a number of years that carcinoma never develops on a healthy mucosa Abnormalities of the gastric mucosa as demonstrated by gastroscopy must therefore be regarded not only as of present but also as of future significance

Among *other gastric tumors* are adenomatous polyps, fibroma fibrosarcoma leiomyoma leiomyosarcoma and lymphoma In some of these cases the gastroscopist can help in establishing the diagnosis and in determining operability Polyps with a long pedicle by x ray may be confused with foreign bodies in the stomach (Fig 17) Gastroscopy will settle quickly the question by direct inspection Gastroscopy in other cases will show the nature of the basal attachment of the tumor whether small and pedunculated as in benign polyp or broad and sessile as in malignant adenomatous polyp Long finger like polyps usually are benign and may be seen readily by gastroscopy Whenever any doubt exists resection should be performed for adenomatous polyps tend to become malignant[6] The surface of the tumor can be studied also by gastroscopy and observation made as to the presence or absence of ulceration and as to whether the tumor is mucosal or submucosal In a recent case diagnosed at another clinic as probable carcinoma gastroscopy showed the tumor to be entirely submucosal except for one small ulceration on its surface (Fig 18) A gastroscopic diagnosis of neurofibroma or fibromyoma was made This patient was operated upon the tumor removed and a pathological report obtained of neurofibroma It might be argued that differentiation between carcinoma and neurofibroma is chiefly of academic interest for in either case surgery is indicated This would perhaps be true in some cases but untrue in others, and in this particular case the differentiation was particularly important because the patient a physician had determined to refuse surgery if the diagnosis had been cancer Thus we see not only the importance of an exact differential diagnosis in any given case but

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CHAPTER II-B

PERITONEOSCOPY

By EDWARD B BENEDICT

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Peritoneoscopy is the direct inspection of the abdominal and pelvic cavities by an endoscopic instrument The procedure dates back to 1901 when Kelling[1] first demonstrated what he called koelioskopie in a dog The method was used later by him in human beings but only to a limited extent From 1910 to 1914 Jacobaeus published several papers on laparo thoracoscopy citing the usefulness of the method in cirrhosis syphilis Pick s disease metastatic tumors and tuberculous peritonitis A comprehensive review of the literature was published by Nadeau and Kampmeier[3] in 1925 Recent interest in the subject has been stimulated by the work of Ruddock[4 5 6] who has developed an improved instrument for peritoneoscopy Other names have been applied to the procedure including celioscopy ventroscopy laparoscopy organoscopy abdominoscopy and splanchnoscopy Peritoneoscopy however seems to be the most generally accepted and most satisfactory term For a more complete review of the literature the reader is referred to recent articles by Ruddock and by Benedict[7 8]

INSTRUMENT

During the early days of peritoneoscopy cystoscopes were used frequently These however were not altogether suitable and a special per

Relative Advantages of Peritoneoscopy and Exploratory Laparotomy

Peritoneoscopy under certain favorable conditions will eliminate the necessity of exploratory laparotomy Owing to definite limitations how ever it never can replace entirely abdominal exploration The procedure is so comparatively easy and safe and gives so much valuable information that in certain instances it may not only be used instead of exploratory laparotomy but may also be used as a preliminary diagnostic measure to surgical procedures While exploratory laparotomy is a major operation usually performed under general anesthesia through a long incision re quiring two weeks hospitalization and involving considerable risk and discomfort peritoneoscopy is a minor procedure performed under local anesthesia through a 1 cm incision requiring only one day s hospitaliza tion and involving very little risk or discomfort

Indications

Peritoneoscopy may be indicated in any abdominal or pelvic condi tion where the diagnosis is obscure or where additional evidence is needed to confirm a diagnosis or to plan treatment The procedure has been found useful in malignant disease cirrhosis tuberculous peritonitis ascites abdominal and pelvic tumors ectopic pregnancy and ovarian dys function In selecting cases for peritoneoscopy it must be borne in mind that the view is limited to peritoneal surfaces and that organs or masses which are situated deeply may be seen only on certain aspects or may be impossible to visualize An instrument recently described by Robin son and Fiske[9] for the purpose of retracting the viscera during peritone oscopy may prove useful

In a review of my own 300 peritoneoscopies nearly half were per formed to determine the presence of carcinoma Of these a large propor tion had their primary source in the stomach many in the ovary some in the colon or rectum others scattered about in various parts of the body Metastatic carcinoma in the liver or generalized abdominal car cinomatosis has been a frequent finding In the differential diagnosis of liver disease that is cirrhosis versus metastatic carcinoma and in dif ferentiating other causes of unexplained ascites notably malignancy and tuberculous peritonitis peritoneoscopy has been extremely helpful The nature of large abdominal tumors has been established Lymphoma sar coma and sarcoid (Fig 17) have been recognized

itoneoscope devised by Ruddock has proved to be very satisfactory The instrument consists of the following parts (1) a small blunt trocar and hand bulb for the purpose of preliminary introduction and inflation of the peritoneal cavity with air (2) a large, blunt trocar with sheath through which (3) the observation telescope with foroblique lens may be intro duced (4) suction apparatus for removal of ascitic fluid (5) small tele scope with biopsy forceps (6) diathermy attachment for the purpose of hemostasis following biopsy

TECHNIQUE

The patient is prepared as for any laparotomy including abdominal shave and scrub fasting stomach empty bladder and preliminary seda tion with barbiturates and morphine The instrument is sterilized in a formalin cabinet The surgeon and his assistants observe the same asep tic precautions as for any abdominal operation The usual site of punc ture is in the midline just below the umbilicus but other sites may be advisable when lower abdominal adhesions or tumors are su pected Pre vious laparotomy scars are to be avoided Novocain is injected into the area selected the skin and subcutaneous tissues being infiltrated down to the peritoneum

A 1 cm stab incision then is made through the skin and fascia and the small blunt trocar is introduced into the peritoneal cavity care being taken not to direct it toward the vertebræ because of the danger of com pressing and injuring the viscera The peritoneal cavity then is in flated with air with an ordinary hand bulb Failure to introduce the trocar deeply enough may result occasionally in accidental inflation of the subcutaneous tissues with air Such an emphysema while not to be desired has never caused any serious trouble in any case in my experi ence

Having obtained a good air space it is safe to introduce the large trocar into the peritoneal cavity The obturator then is removed from the sheath and the telescope is inserted in its place The secret of success in peri toneoscopy lies in having a large peritoneal air space in order to assure satisfactory visualization The examination of the abdomen and pelvis should be carried out systematically The Trendelenburg position and other changes of position may be very helpful in exposing the various organs to be examined Rectal or vaginal palpation by an assistant may aid in ex posure (Fig 16) Another assistant should be present to watch the pa tient's pulse respiration blood pressure and general condition in order to prevent any mishap

with a prolonged prothrombin time die of hemorrhage eight days after liver biopsy for extensive metastatic carcinoma of the liver and another death three weeks after perforation of the large bowel in a severely ill patient proven by peritoneoscopy to have advanced tuberculous peritonitis This patient was operated upon immediately and the perforation closed but the combination of an advanced widespread tuberculous peritonitis and perforation of the large bowel was too much for him to withstand The mortality rate in this series therefore is 1 per cent Olim[10] has reported also a death from perforation of a small cholangitic abscess with the biopsy forceps in a case of carcinoma of the pancreas with peritoneal and mediastinal metastases These deaths should not be regarded as unduly disturbing for they all occurred in patients suffering from incurable diseases With greater care in the selection of cases and strict insistence on a normal prothrombin time the mortality rate certainly should be below 1 per cent In order to arrive at the same diagnosis without peritoneoscopy an exploratory laparotomy would have been necessary and this in itself would carry with it a much higher mortality than 1 per cent For example exploratory laparotomy for inoperable carcinoma of the stomach has a mortality of 15 to 30 per cent depending on the selection of cases The significance of avoiding unnecessary exploratory laparotomy in over 37 per cent of the cases in this series as shown below therefore is very evident

One other accident occurred in this series a perforation of the stomach *in a patient with a previous transverse cholecystectomy scar* Owing to adhesions the peritoneoscope was inserted directly into the stomach Immediate laparotomy showed no leakage had occurred but it was feared some might have taken place had laparotomy been delayed A diagnosis of cirrhosis was made at the same time by surgical biopsy and the patient made an uneventful recovery from these procedures Including the fatal case already mentioned perforation has occurred twice in this series an incidence of 0 67 per cent

Biopsy by Means of the Peritoneoscope

Biopsy specimens when indicated may be obtained in a very high percentage of cases but this should not be attempted in vascular or cystic tumors or in situations where it might result in undue spread of a relatively localized malignant process The biopsy wound should be coagulated with diathermy In my experience serious hemorrhage has occurred only once following peritoneoscopic biopsy This case has been referred to above In jaundiced patients it is advisable to guard against

mors have been found and the diagnosis made by peritoneoscopic biopsy In the pelvis ovarian cysts or other ovarian tumors have been diagnosed or confirmed by peritoneoscopy Ectopic pregnancy ovarian dysfunction pelvic inflammation and other miscellaneous pelvic diseases have been examined and the diagnosis established or confirmed by this procedure

Contraindications

Serious cardiac or pulmonary disease may be a contraindication as the peritoneal distention necessary for a satisfactory examination may somewhat embarrass the circulation or the motion of the diaphragm Numerous abdominal adhesions may constitute a relative contraindication although usually it is possible to select a site for puncture at a safe distance from previous abdominal scars Because of the danger of spreading infection peritoneoscopy is contraindicated in acute inflammatory conditions

Complications

If the above contraindications are observed carefully peritoneoscopy is attended with small risk Elderly people and even patients with some cardiac and pulmonary disease may be examined safely provided an assistant is present constantly to watch the patient s general condition Without this precaution serious cardiac embarrassment may occur Even with the utmost precaution there is always a slight possibility of perforating the bowel in a patient with multiple adhesions With care in avoiding proximity to previous laparotomy scars generally it is possible to select a peritoneal space free of adhesions If however a perforation should occur usually it is found that the bowel is so adherent to th abdominal wall that no leakage will take place Nevertheless immediat laparotomy probably should be performed to prevent any possible soilin of the peritoneal cavity

Accidents

Fatalities from peritoneoscopy are rare Two already have been re ported one a very early case of mine with coronary disease and lun abscesses improperly selected for the examination and not closely watche during the procedure[7] and another reported by Ruddock[4] as a deat from liver biopsy wound in a case with extensive metastatic carcinom of the liver Since my early report I have had one jaundiced patie

with a prolonged prothrombin time die of hemorrhage eight days after liver biopsy for extensive metastatic carcinoma of the liver and another death three weeks after perforation of the large bowel in a severely ill patient proven by peritoneoscopy to have advanced tuberculous peritonitis This patient was operated upon immediately and the perforation closed but the combination of an advanced widespread tuberculous peritonitis and perforation of the large bowel was too much for him to withstand The mortality rate in this series therefore is 1 per cent Ohm[10] has reported also a death from perforation of a small cholangitic abscess with the biopsy forceps in a case of carcinoma of the pancreas with peritoneal and mediastinal metastases These deaths should not be regarded as unduly disturbing for they all occurred in patients suffering from incurable diseases With greater care in the selection of cases and strict insistence on a normal prothrombin time the mortality rate certainly should be below 1 per cent In order to arrive at the same diagnosis without peritoneoscopy an exploratory laparotomy would have been necessary and this in itself would carry with it a much higher mortality than 1 per cent For example exploratory laparotomy for inoperable carcinoma of the stomach has a mortality of 15 to 30 per cent depending *on the selection of cases* *The significance of avoiding unnecessary exploratory laparotomy* in over 37 per cent of the cases in this series as shown below therefore is very evident

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bleeding by the administration of vitamin K until the prothrombin time is normal

The importance of biopsy hardly can be overestimated for no matter how expert the observer may be in the diagnosis of gross pathology occasional mistakes are bound to occur if a microscopic section is not examined This has been emphatically brought home to me in three cases of tuberculous peritonitis which in the gross appearance exactly simulated multiple carcinomatous implants Biopsy established the correct diagnosis in each case I am told that the gross appearance may be impossible to differentiate even at autopsy In another recent case with a very large abdominal tumor the gross appearance was that of metastatic ovarian implants in the peritoneum but the biopsy showed granuloma and subsequent operation proved an echinococcus cyst of the liver

During the first three years (1936 1937 1938) of peritoneoscopy at the Massachusetts General Hospital biopsy was done in only 14 cases during the last three years (1939 1940 1941) a specimen for biopsy has been obtained in 120 cases (53 6 per cent) In the 134 cases in which a biopsy specimen was obtained the pathological report was positive in 100 negative in 29 insufficient tissue in 5 The positive pathological reports are divided as follows carcinoma 70 cirrhosis 21 tuberculosis 4 hepatitis 2 sarcoid 1 sarcoma 1 granuloma 1

Evaluation of the Method

Any safe and easy method of diagnosis which provides information not obtainable in any other way is certain to be useful Peritoneoscopy is such a method Because of limitations already referred to it can replace exploratory laparotomy only in certain cases When for example metastatic malignancy is proven by peritoneoscopy exploratory laparotomy usually is unnecessary In elderly patients and others who are poor surgical risks the clinician may hesitate to recommend exploration for diagnostic purposes and yet be very glad to have a positive diagnosis by peritoneoscopy In evaluating the method it has been found convenient to group the cases as follows

Laparotomy Avoided —In this group are placed the patients who probably would have been explored if they had not been subjected to peritoneoscopy When for example a patient enters with ascites and ovarian malignancy is suspected frequently it is possible to save a laparotomy by finding very widespread malignant disease at peritoneoscopy Or in the case of a gastric carcinoma without obstruction the finding of metastatic nodules in the liver or peritoneum will be a contraindication

to surgical operation Patients in the past have been explored to establish a diagnosis in unexplained ascites or to differentiate the various causes of an enlarged liver Such exploratory operations are no longer necessary In the category of laparotomy avoided are placed 112 cases or 37 3 per cent

Purpose Fulfilled — Peritoneoscopy should be undertaken with an express purpose in mind as for example to confirm a clinical diagnosis to exclude metastatic malignancy to inspect an abdominal mass or to determine the cause of ascites When this purpose has been accomplished successfully the case may be grouped under purpose fulfilled Such examinations may be positive or negative but in all cases in this group helpful information was given to the internist in the management of the patient or to the surgeon in deciding for or against further operative procedures In this series the purpose of the examination has been fulfilled in 279 cases or 93 per cent

Diagnosis Changed — When the clinician puts down three or four tentative diagnoses it is unusual for the peritoneoscopist to reveal an entirely unsuspected condition However this has happened occasionally as for example clinically so called unexplained ascites has proven at peritoneoscopy to be a large soft hemangio arcoma carcinoma of the stomach supposedly with liver metastases has turned out to be carcinoma of the stomach with cirrhosis of the liver gastric neoplasm with unsuspected pelvic pathology has been shown to have in addition an ovarian cyst clinical lymphoma has proven to be carcinoma A striking example of the value of peritoneoscopy is the following case of ascites thought to be *due to metastatic disease from an earlier carcinoma of the breast* but demonstrated at peritoneoscopy to be due to bilateral malignant papillary cystadenomata of the ovaries In this case the endoscopist felt that the tumor could be removed though probably only as a palliative procedure This was accomplished successfully a few days later x ray treatment given and the patient survived comfortably for over a year Without the benefit of peritoneoscopy this patient might well have been considered to have had hopeless recurrent carcinomatosis In this group there are 11 cases or 3 7 per cent

Failures — Occasionally the purpose of the examination is not fulfilled *and therefore failure is recorded* Failures are due almost wholly to widespread adhesions rendering manipulation dangerous or impossible Inability to visualize satisfactorily both ovaries may also make the examination incomplete Failures will be comparatively few if the limitations of the method are kept in mind Only 9 cases 3 per cent should be recorded in this group

Errors — As with any procedure a few errors are unavoidable If a satisfactory biopsy has been obtained from the right location, errors are practically eliminated but biopsy is not always possible Serious mistakes have not been made but partial or complete errors have occurred as for example failure to distinguish benign from malignant tumors In two instances malignant nodules in the liver have been overlooked as proven by subsequent laparotomy in one of these cases only a single nodule was present and was located in an inaccessible part of the liver in the other case nodules were seen but were beneath the surface and were misinterpreted A complete error occurred recently when a circumscribed movable pulsating mass was thought to be a benign tumor of retroperitoneal origin with transmitted pulsation Operation however, proved the mass to be an aortic aneurysm Aneurysm had been strongly considered clinically but in the absence of positive serology, history of syphilis or trauma tumor also had been considered possible The fact that this mass was retroperitoneal made the diagnosis impossible by peritoneoscopy Errors in some cases of this sort are due simply to inherent limitation of the method Twelve cases belong in this group 4 per cent

Analysis of Results

Analysis of 300 peritoneoscopies performed by the author at the Massachusetts General Hospital since 1936 reveals the following facts 293 patients have been examined a few of them more than once There were 137 males 156 females Most of the patients have been between 40 and 70 years of age but four were under 20 the youngest 12 years old the oldest 90 Peritoneoscopy has been performed successfully in a baby of 18 months[4] The youngest in my series was examined for question of tuberculous peritonitis and this disease was excluded by peritoneoscopy The patient 90 years of age was studied for question of ovarian tumor and an ovarian cyst (Fig 1) was found Because of the patient s age this cyst was drained at a subsequent peritoneoscopy[7]

Carcinoma — One hundred and fifty five examinations were carried out for question of carcinoma and in 131 84 5 per cent the diagnosis was established by peritoneoscopy In many of these cases a diagnosis of carcinoma had been suspected clinically and was confirmed at peritoneoscopy In others the examination disclosed the extent of the disease and aided in determining the operability of the lesion

By far the largest group were those with a clinical diagnosis of carcinoma of the stomach (Fig 2) who were examined to determine the presence or absence of liver (Figs 3 and 4) or peritoneal metastases


Fig 1


Fig 2


Fig 3


Fig 4

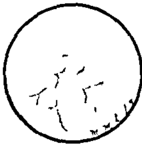

Fig 5


Fig 6


Fig 7


Fig 8


Fig 9

Fig 1 Benign ovarian cyst diagnosis estal l shed by peritoneoscop y and cyst drained by trocar a piration see text

Fig 2 Ca cinoma of stomach adherent to liver The tumor has invaded the serosa of the stomach

Fig 3 Metastatic carcinoma of li er In the upper part of the field are seen two typical um bil cated carcinomatous lesions on the anterior surface The sharp normal liver edge is seen in the middle of the illust ation

Fig 4 Metastatic carcinoma of liver close up view of typical large umbilicated carcinomatous nodule

Fig 5 Ovarian carcinomatosis characteristic translucent cyst l ke implants on the peritoneum

Fig 6 Carcinoma of pancreas with cy tic projection of tumor mass through the gastro-hepatic omentum

Fig 7 Distended gall bladder with normal liver edge in the background in a case of carcinoma of the pancreas. Patient entered complaining of jaund ce and loss of eight Physical exam nation sh wed a mass n the right upper quadrant ? di tend d gall bladder ? metastat c carcinoma n the liver Peritoneoscopy disclosed a normal liver vith a distended gall bladder Cholecystenterostomy was performed later

Fig 8 Metastatic sarcoma of l ver Note cystic masses on ante ior surface

Fig 9 Metastatic melanotic sarcoma of l ver Patient had had a p evious eye enucleation for melanotic sarcoma Positive bi psy obtained from recurrent les on in liver

In this group 67 cases were studied in 55 of which a correct interpretation of operability was made Owing to inability to demonstrate retroperitoneal glands by peritoneoscopy 8 cases were found to be inoperable at laparotomy In one of the early cases done in 1937 peritoneal metastases were seen in the anterior peritoneum overlying the stomach but were misinterpreted

The next largest groups of cases were those examined for question of carcinoma of the ovary (Fig 5) 27 cases of the liver (primary source undetermined) 24 cases of the colon and rectum 11 carcinomatosis (primary source undetermined) 7 of the pancreas (Figs 6 and 7) 5 of the esophagus 4 of the bronchus 3 of the breast 3 of the gall bladder 2 of the kidney and adrenal 1 each

Sarcoma — Fifteen cases of sarcoma (Figs 8 9 and 10) have been examined in 14 of which the diagnosis was established or confirmed by peritoneoscopy In one case an error was made owing to failure to take a biopsy specimen

Lymphoma — Six cases of lymphoma have been studied in all of which a positive diagnosis was made by peritoneoscopy

Cirrhosis — As previously stated peritoneoscopy is of great value in the study of liver disease especially in the differential diagnosis between malignancy and cirrhosis (Figs 11 and 12) Forty three cases have been placed in this group and in 39 90 7 per cent of these the diagnosis was established or confirmed by peritoneoscopy Only one partial error was made in this group and this was due to failure to take a biopsy specimen Twenty five biopsy specimens were obtained and reported as biliary alcoholic atrophic or toxic cirrhosis hepatitis and bile stasis These reports have helped materially in the management of the patients and in our knowledge of liver disease

Ectopic Pregnancy — In this series only 6 cases have been examined for question of ectopic pregnancy (Fig 13) too few for any conclusions to be drawn Ruddock[6] reports 58 cases examined for ectopic pregnancy with a clinical accuracy of only 50 per cent but a peritoneoscopic accuracy of 100 per cent Hope[11] has reported 10 cases in which he feels peritoneoscopy was a helpful adjunct to other methods of examination

Tuberculous Peritonitis — Thirteen cases have been examined for tuberculous peritonitis (Figs 14 and 15) with the following results positive 10 cases (4 with biopsy) negative 3 In three of those with positive biopsy the diagnosis of tuberculous peritonitis had been unsuspected completely the provisional diagnoses having been as follows (1) ascites ? cirrhosis ? carcinomatosis (2) ascites ? ovarian carcinomatosis (3) ascites ? cirrhosis

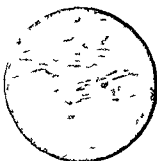


Fig 10

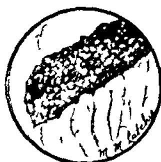


Fig 11



Fig 12

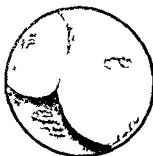


Fig 13

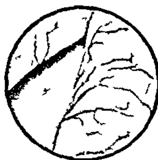


Fig 14



Fig 15

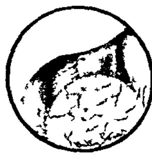


Fig 16



Fig 17

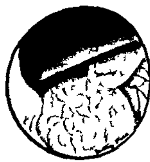


Fig 18

Fig 10 Hemangiosarcoma peritoneoscopic appearance of huge hemangiosarcoma occupyin almost the entire abdomen Patient entered the hospital with diagnosis of ascites but peritoneoscopy disclosed large vascular tumor later successfully resected Patient alive and well now 2 years later

Fig 11 Cirrhosis of liver distant view note typical hob nailed appearance

Fig 12 Cirrhosis of liver close up view characteristic large nodular hob-nailed appearance

Fig 13 Normal pregnancy with ovarian cyst The patient was examined for ? ectopic pregnancy or ovarian cyst Peritoneoscopy disclosed normal pregnancy with ovarian cyst

Fig 14 Tuberculous peritonitis multiple tuberculous implants on the peritoneal surface close to the edge of a normal liver

Fig 15 Tuberculous peritonitis multiple tubercles with adhesions

Fig 16 Small ovarian cyst showing exposure with the aid of assistant s finger in the rect m The clinical diagnosis of this cyst was doubtful Peritoneoscopy established a positive diagnosis.

Fig 17 Sarcoid of liver note striated appearance throughout the surface and edge of liver Patient had a clinical picture consistent with sarcoid and a very much enlarged liver Biopsy of the liver through the peritoneoscope showed sarcoid

Fig 18 Retroperitoneal tumor Physical examination disclosed a mass in the right upper quadrant The differential diagnosis lay between an enlarged liver gall bladder disease or retroperitoneal tumor Peritoneoscopy revealed a normal liver and gall bladder and showed the mass to be retroperitoneal The indentation at the left of the illustration indicates pressure on the mass by the examiner s hand palpating through the abdominal wall Nephrectomy was carried out later for chronic pyelonephritis and perinephritis

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Gunshot and Stab Wounds — Hamilton[12] has reported 5 cases in which he has found peritoneoscopy a safe and reliable method of determining the presence or absence of hemorrhage or perforation in doubtful cases of gunshot or stab wound The writer has had no experience with such cases but agrees with Hamilton that in very carefully selected cases valuable information might be obtained by peritoneoscopy

Ovarian Dysfunction — In certain cases of ovarian dysfunction peritoneoscopy has given helpful information regarding the presence of normal or atrophic ovaries or ovarian tumors (Fig 16) Nine patients in this group have been studied, in 8 of whom the examination was helpful though not always conclusive Two patients with amenorrhea were found to have atrophic ovaries and infantile uterus In a third patient no ovaries or uterus could be demonstrated in spite of an excellent visualization of the pelvis In one case the ovaries could not be visualized satisfactorily

Sterilization — By means of a special electrode, introduced through the peritoneoscope it may be possible to produce sterility by fulguration of the Fallopian tubes In a preliminary report Power and Barnes[13] call attention to this method and present pathological material from both human and animal subjects to demonstrate its effectiveness in the production of tubal occlusion No data however are as yet available Ruddock[14] and Anderson[15] also have suggested the possibility of this method of sterilization but all peritoneoscopists including the writer, have had difficulty in securing suitable patients

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CHAPTER III

ULCER OF THE STOMACH DUODENUM AND JEJUNUM

By RALPH C. BROWN

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Fig 14 No 5 Wash drawing of stomach of patient described in legend of Fig 14 No 1 whose ulcer is shown in Fig 14 Nos 1 to 5 Two and one half years after ulcer treatment this patient entered the Presbyterian Hospital with virulent pneumonia from which she died This drawing is an exact reproduction of a photograph of the stomach Note the widely radiating lines of cicatricial contracture converging into the large central mass of scar tissue This case strikingly shows that the largest gastric ulcers can be healed and remain healed

having demonstrated the hemorrhagic necrotic origin of ulcer of the stomach and was responsible for the universal acceptance of this view and who also first made use of the term corrosive ulcer of the stomach recognizing clearly the role of the gastric juice in the pathogenesis The greatest impetus to progress in the study of peptic ulcer came from the development of modern aseptic abdominal surgery Prior to this period duodenal ulcer was thought to be an uncommon lesion and gastric ulcer was rarely diagnosed unless associated with massive hemorrhage Trier[3] of Copenhagen had published in 1863 the most important of the early monographs on duodenal ulcer but it was not until as late as 1887 that Bucquoy[9] made clear the fact that the symptoms of duodenal ulcer are sufficiently characteristic to enable a clinical diagnosis to be made The pioneer work of Moynihan and W J Mayo in the field of gastric and duodenal surgery during the first decade of this century supplied a powerful stimulus to clinical investigation and in 1915 Sippy[0] formulated principles for the medical treatment of ulcer, which have proven valid and which have been accorded universal recognition

Etiology

General Incidence — During the nineteenth century the chief sources of information regarding the frequency of occurrence of peptic ulcer were statistics from the great pathologic institutes which showed wide and unexplained divergences In general the figures on gastric ulcer were more nearly in accord with present day statistics whereas duodenal ulcer was believed to be relatively rare It was not until Moynihan s monograph Duodenal Ulcer (1910) focused the attention of the medical profession upon the frequency and major clinical importance of this le ion that the first portion of the duodenum was subjected to sufficiently close scrutiny by the pathologist to bring out over a period of years the accurate statistical information now available True, there are still marked differences due possibly to geographical or racial factors Holzweissig[1] reported on the findings in 3 508 autopsies at Kiel covering a period of 7 years on adults only in which the stomach and duodenum were examined with the greatest care Acute or chronic ulcer or ulcer scars were found in the stomach in 6 9 per cent and in the duodenum in 5 3 per cent of these cases In England at the Leeds General Infirmary Stewart found in an intensively studied consecutive series of 1 500 autopsies 130 cases of acute, subacute and chronic ulcers equally distributed between the stomach and duodenum (4 5 per cent in each) In addition to this large percentage of active ulcers Stewart found 42 cases having gastric ulcer scars and 36 cases in which there were scars in the duodenum American statistics suggest a somewhat lower ulcer frequency in this country Portis and Jaffe[13] reporting that in 9 171 consecutive autopsies at the Cook County Ho pital Chicago 19 9

Historical

Recognition of ulcer of the stomach and duodenum as a pathological entity dates from isolated postmortem reports made in the seventeenth and eighteenth centuries, although it is possible that Galen may have been the first to make observations on round ulcer of the stomach Littre[1] described a fatal case of hemorrhage from gastric ulcer in 1704 and in 1735 Morgagni recorded what were probably the first notes on duodenal ulcer The first clear description of the morbid anatomy and symptoms of gastric ulcer was published by Baillie[3] of Edinburgh in 1793 and more complete observations on both gastric and duodenal ulcer, with recommendations as to treatment were made by Abercrombie[4] in 1828 It remained, however, for Cruveilhier to present in his admirable Anatomie Pathologique du Corps Humain, etc (Paris T I, 1829 1835) the classical descriptions which form the foundations of our present knowledge of peptic ulcer Cruveilhier was the first to make clear the distinction between simple benign ulcer of the stomach and cancer

Other distinguished names in the history of the development of knowledge of the disease are those of Rokitansky[5], who in 1842 made one of the early important contributions to the German literature and, far in advance of his time was the first to advocate the neurogenic origin of ulcer, Brinton[6] and Virchow[7], the latter

having demonstrated the hemorrhagic necrotic origin of ulcer of the stomach and was responsible for the universal acceptance of this view and who also first made use of the term corrosive ulcer of the stomach recognizing clearly the role of the gastric juice in the pathogenesis The greatest impetus to progress in the study of peptic ulcer came from the development of modern aseptic abdominal surgery Prior to this period duodenal ulcer was thought to be an uncommon lesion and gastric ulcer was rarely diagnosed unless associated with massive hemorrhage Trier[8] of Copenhagen had published in 1863 the most important of the early monographs on duodenal ulcer but it was not until as late as 1887 that Bucquoy[9] made clear the fact that the symptoms of duodenal ulcer are sufficiently characteristic to enable a clinical diagnosis to be made The pioneer work of Moynihan and W J Mayo in the field of gastric and duodenal surgery during the first decade of this century supplied a powerful stimulus to clinical investigation and in 1915 Sippy[10] formulated principles for the medical treatment of ulcer, which have proven valid and which have been accorded universal recognition

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to 1936, there were 457 cases of all types of peptic lesions, approximately 5 per cent less than one half the incidence shown in the reports from English and German sources The Philadelphia General Hospital figures 22,936 autopsies in the period 1920–1937, were still lower, showing active peptic ulcer in 2 7 per cent of cases according to a survey by Gordon and Manning[14] They report no racial difference in incidence between white and colored patients Hurst[1] concludes from a study of autopsy statistics that it may be assumed that about 10 per cent of all individuals have ulcer of the stomach or duodenum at some time during life This may be accepted as a conservative estimate

It is highly probable that peptic ulcer is increasing in frequency, Henry A Christian[7] reporting a fourfold increase in the incidence of gastric and duodenal ulcers in the wards of Peter Bent Brigham Hospital, Boston, during the period 1914 to 1929 The most striking evidence has come recently from military hospitals

Col William Brockbank[1] points out that in the war 1914–1918 "inflammation and ulceration of the stomach occupied twelfth place in the order of incidence of diseases whereas in both the British and American armies it is now one of the chief causes of medical disability A series of 931 consecutive cases of dyspepsia admitted to a British military hospital during the first 18 months of the present war represented 8 3 per cent of all admissions Of these 397 cases, 42 5 per cent were diagnosed ulcer Relatively few of these cases had acquired ulcer after induction into military service H Tidy[18] states that the prevalence of dyspepsia organic and non organic in the army in the present war is a reflex of its incidence in the civilian population which in his opinion has increased greatly in the last 20 years He also finds no evidence of undue development of fresh cases of peptic ulcer in the British Army Of admissions to British military hospitals in 1942 for peptic ulcer Tidy found that the onset had occurred in civilian life in 81 per cent of the cases and is of the opinion that men suffering from peptic ulcer are not suitable for army service

Inquiry as to the relative frequency of gastric and duodenal ulcer has given rise to much discussion The surgeons observe duodenal ulcer with considerably greater frequency than gastric ulcer Thus Mayo[14] reported that in the years 1906–1920 there were operated on at the Mayo Clinic 1 191 patients with gastric ulcer and 4 532 patients with duodenal ulcer, a proportion of 1 to 4 On the other hand the pathologists find a somewhat greater proportion of ulcer and ulcer scars in the stomach the combined figures of Holzweissig, Musa and Hart show a proportion of 1 16 gastric to 1 duodenal ulcer in a large and very carefully observed postmorten material

This divergence in the figures from surgical and autopsy sources undoubtedly is due to the fact that duodenal ulcer is more likely to cause symptoms sufficiently

distressing to compel the patient to seek medical or surgical relief whereas gastric ulcer frequently pursues a relatively latent clinical course

Sex Incidence — Statistics from many sources show that gastric ulcer occurs with almost equal frequency in men and women but all authorities are unanimous in recognizing that duodenal ulcer is far more common in men than in women the proportion being about 3 to 1 Thus in 9 000 autopsies at the Leeds General Infirmary the ratio of acute and chronic duodenal ulcer in men in comparison to women was 3 05 to 1 Practically the same ratio is found in the clinical reports of the Presbyterian Hospital Chicago series

Age Incidence — Peptic ulcer occurs in infants and young children far more frequently than is generally recognized The writer has observed massive hemorrhage in a robust boy of 3 years of age with x ray deformity of the duodenal cap, typical chronic duodenal ulcer of hemorrhagic type with extensive scar tissue deformity in the cap in a boy of 5 years and a similar lesion originating at the age of 9 which at the age of 14 had caused almost complete cicatricial stenosis of the duodenum

Bird Limper and Mayer [0] collected 119 cases in which operations had been performed for peptic ulcer in infants and children and an additional 124 non operated cases in most of which the diagnosis was made at autopsy A review of case records indicated a marked tendency to hemorrhage and perforation in ulcer occurring in the first two weeks of life with no evidence of intracranial injury except in a few cases

The ratio of duodenal to gastric lesions in this age group was 2 to 1 As age advances beyond the seventh year there is a rise in the number of cases that are recognized and an increased tendency to pyloric stenosis and to perforation Over 70 per cent of the cases recorded between the ages of 7 and 15 were operated upon It is probable that many children in this age group have ulcer causing symptoms erroneously diagnosed chronic appendicitis mesenteric lymphadenitis or neurosis

Familial Predisposition — Family predisposition to peptic ulcer undoubtedly exists Careful inquiry into the family history of ulcer patients discloses either positive or presumptive evidence of ulcer in several members of the family in a remarkable percentage of cases Edwards and Copeman [1] made such a study in 139 cases in an army ho pital finding a family history of ulcer in more than one half of the cases

Seasonal Occurrence — Occurrence of ulcer symptoms during spring and autumn is difficult to explain Formerly when greater stress was placed on infection in the pathogenesis of ulcer than at present it was cited as evidence of the role played by bacteria Such a seasonal incidence is found to be a feature in a definite although not large proportion of ulcer patients

Pathogenesis

Role of Hydrochloric Acid in Ulcer Pathogenesis

There is a general acceptance of the concept that ulcer of the stomach and duodenum forms as a result of a local loss of resistance on the part of the mucous membrane to the digestive action of the gastric juice Why this should occur in one individual and not in another is a question for which there is yet no wholly satisfactory answer although a flood of light has been thrown on the mechanism of ulcer formation by a great volume of fundamental experimental work during the past twenty years

Ulcer occurs in those portions of the alimentary tract in which the mucous membrane is exposed to contact with acid gastric juice Thus ulcer is formed in the stomach and in the first portion of the duodenum Beyond the duodenal bulb the acid chyme is rapidly neutralized by the alkaline secretions of the pancreas and duodenal glands and ulcer does not occur When the mucosa of the jejunum is exposed to the peptic action of gastric juice by gastroenterostomy, ulcer forms within the first two inches of either the efferent or afferent loop of the jejunum with such frequency that resection of the acid bearing portion of the stomach has superseded gastroenterostomy in the surgical treatment of ulcer in many hospitals Much more rarely does peptic ulcer occur in the lower portion of the esophagus in individuals usually gravely ill in whom impaired cardiac sphincter function permits the frequent regurgitation of gastric juice into the esophagus Also to be noted is the occurrence of ulcer in the ileum adjacent to a Meckel s diverticulum containing gastric mucosa secreting hydrochloric acid

The early attempts to produce chronic peptic ulcer in laboratory animals were many and varied including trauma of the mucosa by cautery and by corrosive chemicals, by excision of portions of the mucosa by ligation of the gastric vessels and by injection into the vessels of lead chromate fat and bacterial cultures Lesions, thus caused, heal invariably and rapidly, proving that there must be some factor in ulcer formation other than the peptic action of a gastric juice which is normally buffered by swallowed saliva food, the mildly alkaline secretion of the antrum, the large amount of mucus secreted by the stomach and by the regurgitation into the stomach of alkaline duodenal contents

The notable work of Mann and his associates in 1923 opened up a new field for experimental investigation and not only demonstrated a means of producing typical chronic duodenal ulcer in dogs but proved the vital importance of th neutralizing effect of the alkaline duodenal content in preventing the formation of duodenal ulcer This was done by sectioning the pylorus, closing the distal end and then dividing the jejunum beyond the ligament of Trietz The distal end of

the jejunum was anastomosed to the pylorus and the proximal end to the ileum near the ileocecal valve thus diverting to the lower ileum the alkaline juices of the pancreas and duodenal glands as well as the bile. Progressive peptic ulcer formed approximately three-quarters of an inch beyond the pylorus in 90 per cent of the dogs thus operated upon.

This proof of the vital role played by acid gastric juice ... investigation of the physio-pathological conditions under which ulcer formation may occur. Outstanding work in this field has been carried on for many years by Dragstedt [a] who, working on the basis of the fact that pure gastric juice is capable of digesting, and thus destroying, all living tissues, investigated the effect of pure fundic gastric secretion in Pavlov pouch dogs. Larger volumes of ... fered gastric secretion were obtained by isolating the entire stomach from continuity with the esophagus and duodenum. In some of these isolated stomachs the nerve supply was left intact, in others the vagi were severed. In this manner a fundus secretion ranging in 24 hours volume from 1,500 c.c. to ... c.c., consisting almost entirely of a water solution of HCl and pepsin and with an almost constant concentration of HCl of about 135 clinical units, was obtained. In the great majority of these dogs a large, sharply punched-out ulcer developed in the middle part of the stomach, with massive hemorrhage or perforation and peritonitis as common terminal events.

Furthermore, Dragstedt states "organs such as the spleen, the kidney, the pancreas, the omentum and the intestinal serosa may be subjected to the digestive action of pure gastric juice by implanting them into defects in the walls of isolated Pavlov or Heidenhain accessory stomachs or in totally isolated stomachs. When this is done, the transplant becomes promptly excavated by the digestive action of the gastric juice and death from hemorrhage takes place in a few days. The contrast with the almost complete immunity from digestion of such tissues implanted into similar defects in normal stomachs is striking and shows that pure gastric juice has a marked aggressive action on living tissue, while the gastric content is relatively inert."

From this experimental work Dragstedt concludes that in the Pavlov pouch and isolated stomach dogs described, gastric ulcer forms as a result of the exposure of the gastric mucosa to a continuous hypersecretion of very highly acid gastric juice. Conversely, that under normal conditions the gastric wall is not digested because it is *not exposed to pure unbuffered gastric juice in continuous hypersecretion*, since during the diurnal periods when the stomach is empty the fasting stomach secretion is very low in volume (10 c.c. to 50 c.c.) and relatively low in free acid content.

That excessive continued secretion of gastric juice may be an important factor in ulcer pathogenesis in man also is strikingly shown by the work of Winkelstein

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Role of Hydrochloric Acid in Ulcer Pathogenesis

There is a general acceptance of the concept that ulcer of the stomach and duodenum forms as a result of a local loss of resistance on the part of the mucous membrane to the digestive action of the gastric juice Why this should occur in one individual and not in another is a question for which there is yet no wholly satisfactory answer although a flood of light has been thrown on the mechanism of ulcer formation by a great volume of fundamental experimental work during the past twenty years

Ulcer occurs in those portions of the alimentary tract in which the mucous membrane is exposed to contact with acid gastric juice Thus ulcer is formed in the stomach and in the first portion of the duodenum Beyond the duodenal bulb the acid chyme is rapidly neutralized by the alkaline secretions of the pancreas and duodenal glands and ulcer does not occur When the mucosa of the jejunum is exposed to the peptic action of gastric juice by gastroenterostomy, ulcer forms within the first two inches of either the efferent or afferent loop of the jejunum with such frequency that resection of the acid bearing portion of the stomach has superseded gastroenterostomy in the surgical treatment of ulcer in many hospitals Much more rarely does peptic ulcer occur in the lower portion of the esophagus in individuals, usually gravely ill in whom impaired cardiac phincter function permits the frequent regurgitation of gastric juice into the esophagus Also to be noted is the occurrence of ulcer in the ileum adjacent to a Meckel s diverticulum containing gastric mucosa secreting hydrochloric acid

The early attempts to produce chronic peptic ulcer in laboratory animals were many and varied including trauma of the mucosa by cautery and by corrosive chemicals by excision of portions of the mucosa by ligation of the gastric vessels and by injection into the vessels of lead chromate fat and bacterial cultures Lesions, thus caused heal invariably and rapidly proving that there must be some factor in ulcer formation other than the peptic action of a gastric juice which is normally buffered by swallowed saliva food the mildly alkaline secretion of the antrum the large amount of mucus secreted by the stomach and by the regurgitation into the stomach of alkaline duodenal contents

The notable work of Mann and his associates in 19 3 opened up a new field for experimental investigation and not only demonstrated a means of producing typical chronic duodenal ulcer in dogs but proved the vital importance of the neutralizing effect of the alkaline duodenal content in preventing the formation of duodenal ulcer This was done by sectioning the pylorus closing the distal end and then dividing the jejunum beyond the ligament of Trietz The distal end of

Nervous System in Ulcer Pathogenesis

General recognition of the fact that the nervous system plays an important and probably fundamental role in the pathogenesis of peptic ulcer was somewhat delayed in this country due largely to our pre occupation with focal infections and the rather wide acceptance of the concept of streptococcal blood stream infection as a major etiological factor It is noteworthy that as early as 1841 Rokitansky [8] described acute perforating ulcers hemorrhagic erosions and simple chronic ulcer for which he stated the proximate cause may be looked for in diseased innervation of the vagus and to extreme acidification of the gastric juice Thirty years ago G von Bergmann published a number of papers on the neurogenic origin of ulcer, stating his belief that on the basis of a constitutional vegetative nervous system imbalance, there occurs spasm of the gastric musculature with resulting local ischemic necrosis and peptic ulcer formation Many authorities have supported this viewpoint including Eppinger and Hess [8] and J Kaufmann [9] Hart[30] was of the opinion that an ischemia resulting from vasomotor disturbance causing arterial spasm is the most important factor in the causation of peptic ulcers

As time passed there appeared many case reports of lethal gastric hemorrhage and perforation associated with brain tumors and following injuries and operations on the brain especially those involving the mid brain Cushing[31] published a classic review of this field of investigation in 1932 recording 3 fatal cases of acute perforating peptic ulceration after cerebellar tumor operations in one case the necrosis being limited to the duodenum in another to the stomach and lower esophagus and in the third to the lower esophagus alone Grant[3] and others have reported similar fatal cases after cerebellar tumor operations Also there are numerous reports of gastric lesions produced experimentally in different species of animals by traumatizing the mid brain area in various ways and by stimulation of the vagus

A connecting link correlating experimental work on the possible major importance of continued hypersecretion with evidence regarding the neurogenic origin of ulcer is supplied by recent interesting studies by Wolf and Wolff [5] in an individual with a gastric fistula studies which show that certain emotional reactions are capable of causing hypersecretion in the stomach comparable to that resulting from prolonged absorption of histamine Their subject was a man aged 56 who at the age of 9 suffered cicatricial occlusion of the esophagus from drinking a scalding fluid About the stoma of the gastrostomy was a protruding collar of gastric mucosa permitting perfect observation of changes in the mucous membrane under varying conditions It was observed that periods of intense, sustained anxiety or of hostility and resentment on the part of the patient were accompanied

Varco, Code and Wangensteen [4], who succeeded in causing continuous stimulation of the gastric glands for a considerable period of time by implanting histamine imbedded in beeswax beneath the skin and in the muscles Typical chronic gastric and duodenal ulcers were produced in the animals thus treated This raises the question as to whether ulcer patients show with any degree of uniformity, an excessive volume of continued secretion during the night hours Actually they do not except in certain cases For many years it has been a routine procedure on the writer's hospital service to empty the stomach of ulcer patients at 9 30 P M and with no food or fluids taken thereafter to again aspirate at midnight for the express purpose of determining the volume of fasting stomach secretion present in a given case

Ordinarily abnormally large volumes of nocturnal, fasting stomach secretion with high acid values are to be found only in cases of long standing pyloric obstruction and in certain large gastric ulcers surrounded by an extensive inflammatory reaction These findings are described in detail in a subsequent section The rapid subsidence of such continued hypersecretion under appropriate management is made clear also

These facts do not rule out the possibility that a temporary state of hypersecretion may have existed in the stomach prior to ulcer formation, an hypothesis supported by the observations of Wolf and Wolff [5], but they do appear to negative the likelihood that some more or less continuous process of formation and absorption into the blood stream of histamine is a factor in the genesis of ulcer in man Further work along the lines suggested by the experiments of Walpole, Varco Code and Wangensteen may alter this viewpoint however

Clinically it has long been known that in general the peptic ulcer individual has higher than normal acid values However reference to Table I will make it clear that normal acidity is relatively common in them and that subnormal acid values are not rare Reports exist of chronic gastric and duodenal ulcer with achlorhydria Exhaustive tests of the secretory function of the stomach should be made before arriving at such a diagnosis The writer has never seen an ulcer case which was acid free to histamine It should also be noted that tests of the secretory function of the stomach frequently reveal hyperacidity of marked degree, free acid of 70 to 80 clinical units in individuals in perfect health

Summarizing these observations on the acid factor in ulcer pathogenesis it is clear that pure fundic secretion is capable of digesting a wide variety of living tissues including the stomach wall The healthy stomach gains immunity to such destructive, corrosive chemical forces by the buffering action already alluded to as well as by the powerful defense supplied by the mucous coating of the mucous membrane It is highly probable that some failure in the functioning of these defensive mechanisms constitutes one of the modes of origin of peptic ulcer

Vascular Factor in Ulcer Pathogenesis

The fact that 82 per cent of gastric ulcers occur on the lesser curvature and in close proximity to it has naturally directed attention to the vascular arrangements and blood supply in this area resulting in several studies made after injecting the arteries Jatrow[33] found that whereas the fundus and greater curvature regions have a good blood supply the vessels supplying the lesser curvature as well as the arterial anastomoses in this part of the stomach wall, are relatively sparse The same condition exists in the lesser curvature part of the first portion of the duodenum From a similar study Reeves[4] concludes that the plexus of vessels in the submucosa on the lesser curvature is made up of much smaller although longer arteries with fewer anastomoses than in other regions of the stomach and that the branches from this plexus pursue a very tortuous course to enter the mucosa

Both stress the probable influence of the contracted state of the empty stomach in diminishing the blood supply in the areas under consideration Reference has been made already to the part played by thrombosis and infarction due to hematogenous infection in the genesis of ulcer Further investigation will be required, however before a definite connection between the anatomical arrangement of the gastric and duodenal arteries and the localization of chronic peptic ulcer is established

Food or Vitamin Deficiencies in Ulcer Pathogenesis

It is improbable that any specific type of food or vitamin deficiency plays a part in the genesis of ulcer However Cheney from his experimental work with chicks supplies some suggestive facts He shows that superficial gastric ulcers in chicks result from withholding from the diet substances which contain an anti gizzard erosion factor, which occurs in close association with but is separate from vitamin K

Similar lesions can be produced by giving the chick cinophen and it is thought that this effect results from toxic action on the liver which in turn interferes with elaboration and storage of the anti ulcer factor and its delivery to the stomach wall

A number of reports have been published indicating that ulcer patients tend to have less than a normal amount of vitamin C in the plasma Thus Riggs[6] and associates observed in 51 ulcer patients a mean of 0 24 mgm per 100 c c of vitamin C as compared with 0 51 mgm per 100 c c in the normal controls It is not suggested however, that a lowered vitamin C is a factor in the pathogenesis of peptic ulcer

by severe and prolonged engorgement of the gastric mucosa and hypermotility and hypersecretion in the stomach In this state erosions of the mucosa and small hemorrhages were caused readily by slight trauma One such small erosion was kept in contact with the patient s gastric juice continually for 4 days, at which time it had increased to 4 mm in diameter and had the punched out appearance of peptic ulcer

Ordinarily the small erosions observed from time to time were quickly covered with mucus and healed within 24 hours A further important observation showed the protective action of mucus in combining with acid in contact with it and thus maintaining the acidity at the mucosal surface at a low level The authors conclude it appears likely then that the chain of events which begins with anxiety and conflict and their associated activity of the stomach and ends with hemorrhage or perforation is that which is involved in the natural history of peptic ulcer in human beings'

While this hypothesis may not readily explain the occurrence of ulcer in in fants and young children or the large group of ulcer cases seen in adolescence, it is quite consistent with clinical experience with peptic ulcer as it occurs in adult patients Emotional stress and strain, prolonged periods of anxiety and the nerv ous exhaustion associated with chronic fatigue have long been recognized as precursors of ulcer and its recurrences Of corrolary significance is the proven beneficent influence of rest of mind and body in the treatment of gastric and duodenal ulcer

Infection in Ulcer Pathogenesis

Acute ulcers of the stomach as well as petechial hemorrhages and hemorrhagic erosions are relatively common necropsy findings in cases of acute septic infection, such as streptococcus viridans endocarditis septic types of scarlet fever, pyemia and septicemia especially that due to acute peritonitis The vomiting of blood has been noted by the writer as a clinical feature in a milk borne epidemic of se vere streptococcus throat infections Hence it is obvious that the initial lesions in peptic ulcer formation may be due either to the localization of pathogenic bac teria in the wall of the stomach causing vascular thrombosis and infarction or to focal necrosis due to bacterial toxins analogous to the acute ulceration of the duo denum associated with severe burns Undoubtedly such lesions may be progres sive and result in chronic gastric and duodenal ulcer Clinically one occasionally sees ulcer symptoms appearing coincident with infection such as acute periapical dental abscess or acute upper respiratory infection but there is no evidence to suggest that infection plays other than a minor role in ulcer pathogenesis in general

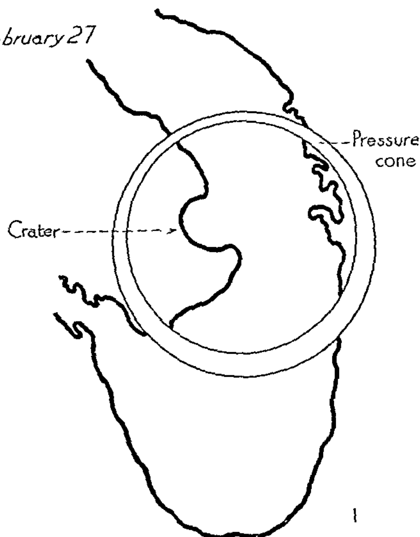


FIG 1 No 1 Contour of x ray film showing ga tric ulcer in a patient Mr S D age 65 who *suffered from recurrent symptoms of chron c gastri and duodenal ulcer over* a period of 40 years associated with continued nocturnal hypersecretion severe nocturnal pain preventing sleep and resultant nervou exhau tion and emaciation

especially in long standing gastric ulcer In estimating the dimensions of such an ulcer from x ray films it should be borne in mind that the apparent depth of the ulcer defect in the film is due in great part to inflammatory *tumefaction of the*

Pathological Anatomy

Peptic ulceration may occur in any mucous membrane exposed to prolonged contact with acid gastric juice, as in the stomach, in the first portion of the duo denum, in the jejunum adjacent to the stoma following gastroenterostomy and rarely in Meckel s diverticulum and in the lower segment of the esophagus where islands of heterooptic acid bearing cells may exist From a pathogenetic viewpoint no distinction should be made between acute peptic ulcer, superficial erosions and hemorrhagic erosions of the gastric mucosa Thus Aschoff[37] described an erosion as a fresh loss of substance of the mucosa, regardless of whether it may have arisen from a disintegration of a circumscribed mucosal necrosis or from a hemor rhagic infarction of the mucosa with secondary digestion " This accurately de fines the initial stage of peptic ulcer formation Acute ulcers vary in size from barely visible superficial erosions to lesions of a centimeter or more in diameter and are more often multiple than otherwise In fatal cases of sepsis the patholo gist may find scores or even hundreds of very small lesions widely distributed In its early phase peptic ulcer has a characteristic appearance tending to a round or oval form with a sharply defined flat margin almost devoid of inflammatory reac tion and with a base varying in appearance according to the depth and the stage of development of the ulcer If very early it may be covered with the brownish black remnants of the hemorrhagic infarct which often precedes ulcer formation Seen at a slightly later stage when all remains of the slough had been digested by the gastric juice, the floor of the ulcer appears clean and smooth

In the early stages of acute ulcer extending into the submucosa some small amount of hemorrhage probably always occurs Soon however, the vessels become blocked by thrombi The tendency of acute ulcer is to heel rapidly and, when healing occurs in one which has not penetrated the muscularis no scar remains When healing fails to take place there is a progressive digestion by the gastric juice of the deeper layers of the stomach wall the muscularis is penetrated, an in flammatory reaction causes elevation of the margins of the ulcer, and at this subacute stage the typical conical crater form becomes apparent Undoubtedly many ulcers heal in this subacute stage extending approximately from the second to the sixth week leaving small white scars However, the longer an ulcer con tinues to be active the less is the tendency to heal and with extension of the inflammatory reaction into the surrounding tissue the chronic stage is reached gradually with active fibroblastic proliferation in the walls and floor of the ulcer, associated with inflammatory edema and engorgement of the blood vessels The inflammatory swelling causes further elevation and inward extension of the mar gins of the ulcer, thus accentuating the excavated crater like appearance of the ulcer defect The crater usually globular in shape may attain great depth,

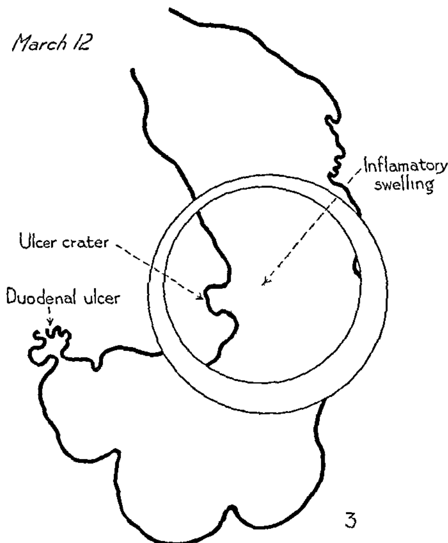


Fig. 1 No. 3 This shows marked diminution between Feb. 27 and March 12 in size of the ulcer crater in the same patient as depicted in Fig. 1 Nos. 1 and 2 due chiefly to lessening of the amount of inflammatory swelling of the margins of the crater of the gastric ulcer. The stippled area shows displacement of barium in the stomach by a *still* considerable inflammatory mass widely surrounding this very chronic ulcer.

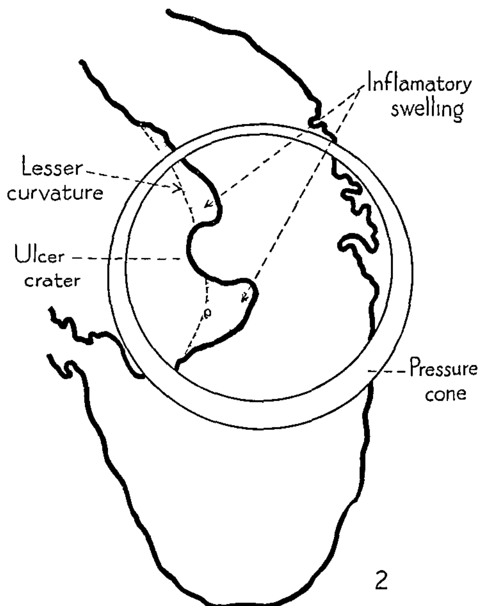


Fig 1 No 2 This shows the same ulcer as shown in Fig 1 No 1 with stippling to indicate the extent of the inflammatory swelling of the wall of the stomach about the ulcer and the usual relation of the base of the ulcer to the lesser curvature of the stomach

stomach wall adjacent to the ulcer (Figs 2 No 1 and 13) Such an inflammatory tumor may attain the size of a large egg with elevation of the margin of the ulcer 1½ to 2 cm above the normal mucosal surface

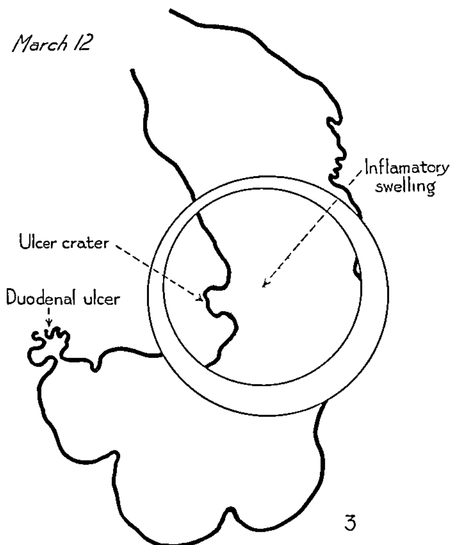


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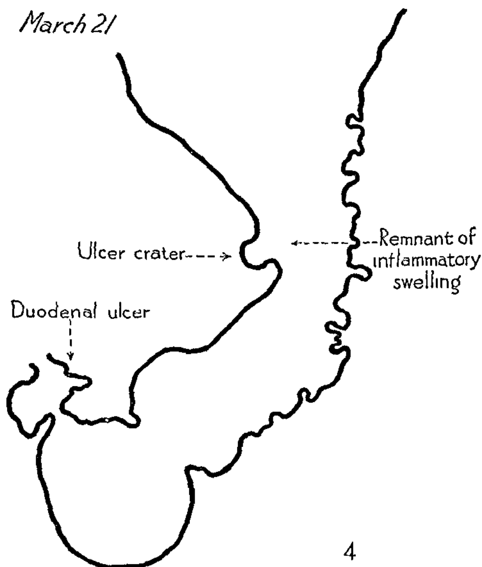


FIG 1 No 4 X ray examination on March 21 9 days later than that shown in Fig 1, No 3 revealing further recession of the inflammatory process

Whereas acute peptic ulcer penetrates *only* the submucosa and subacute ulcer the muscularis chronic ulcer involves and often *breaches* the serosa, the advancing inflammatory exudate bringing about a fusion *of the* base of the ulcer with adjacent structures most commonly with the pancreas *so that* pancreatic tissue frequently forms a part of the floor of the ulcer Since the pancreas is somewhat

resistant to peptic digestion actual invasion of the pancreas always is superficial in extent although a marked degree of localized pancreatitis occurs very commonly in such cases Next in frequency of involvement by the base of an ulcer is the liver which may be deeply eroded The appearance of the serosa forming part of the base of a non penetrating ulcer is characteristic being thickened and opaque with hyperemic vessels and often with bands of adhesions connecting it with neighboring structures, including the gallbladder

Perforation may occur as the initial agonizing symptom of an acute ulcer as well as in chronic ulcer Fortunately statistically this potentially fatal complication is relatively rare a survey of 1 500 consecutive ulcer cases admitted to the Presbyterian Hospital Chicago, showing 33 cases of acute perforation In a very large proportion of cases the site of perforating ulcer is the anterior surface of either the duodenum or the distal part of the stomach this being attributable to the absence in these areas of fixed organs such as the pancreas and liver to which posterior wall duodenal ulcers and lesser curvature gastric ulcers so commonly become adherent An acute perforating ulcer if not closed by early surgery causes general peritonitis In a comparatively small proportion of cases a fibrinous walling off process about the perforation area may be set up with sufficient rapidity to prevent widespread extension of the inflammation The localized peritonitis resulting from such a subacute type of perforation may subside spontaneously or may eventuate in abscess formation requiring surgical operation

As the following table shows the great majority of gastric ulcers are situated along the lesser curvature or in close proximity to it the pyloric region ranking next in frequency Chronic ulcers of the fundus are uncommon and the greater curvature is involved very rarely The writer saw in consultation a very large ulcer of the dependent portion of the greater curvature which was resected because of strong suspicion of carcinoma and proved to be benign (Fig 2) A composite of the postmortem figures in 1 413 cases compiled from various sources by Hauser yields the following topographical distribution

Lesser curvature	587 = 41 54%	
Posterior wall	183 = 12 95%	9 96%
Pars pylorica	359 = 25 4 %	
Anterior wall	82 = 5 80%	
Cardia	78 = 5 52	20 09%
Greater curvature	64 = 4 53	
Fundus	60 = 4 24	

Duodenal ulcers are confined to the first portion the so called duodenal bulb rarely being found more than two inches beyond the pylorus Postmortem records indicate that the anterior wall and the posterior wall are involved with almost equal frequency Two ulcers one on the anterior the other on the posterior

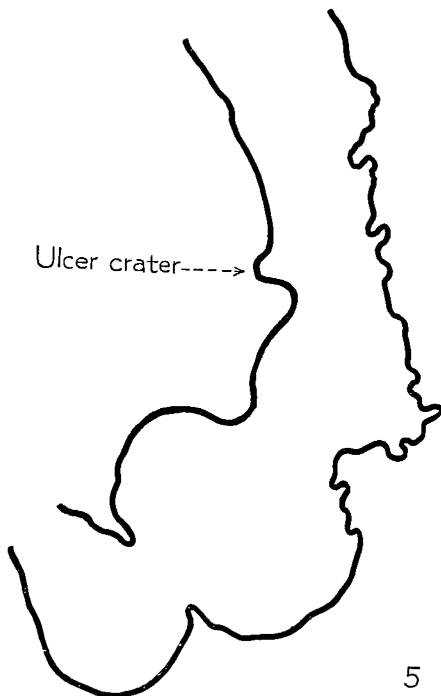


Fig 1, No 5 X ray examination on March 30 9 days following that shown in Fig 1 No 4 revealing still further recession in the process

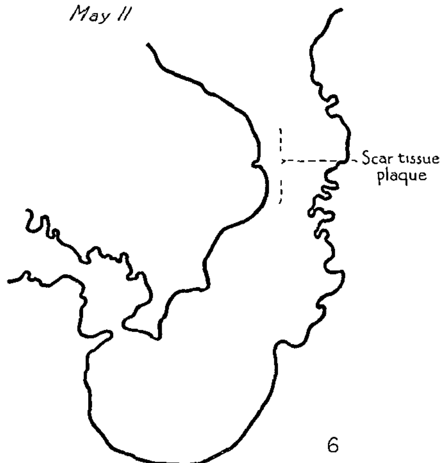


FIG 1 No 6 X ray taken on May 11 of the stomach of the patient described in the legend of Fig 1 No 1 This shows the final healing stage of an extensive scar tissue placque This result was obtained by rigid adherence to the principles of physical re t and acid neutralization including a nocturnal milk drip for 4 weeks

wall are present in a considerable proportion of cases However there is a marked tendency for anterior wall duodenal ulcers either to perforate or to heal whereas posterior wall ulcers have a far greater tendency to chronicity especially so when the base of the ulcer is adherent to the pancreas with resulting difficulty in in folding and healing The *proximal margin of duodenal ulcer may extend* close up to the pylorus but usually as in the typical chronic duodenal ulcers produced *experimentally by Mann and his associates it lies from one quarter to*

three quarters of an inch from the pylorus Chronic peptic ulcers usually are single However pathological records show that in approximately 25 per cent of cases two or more ulcers or ulcer scars are present, and both stomach and duodenum are affected in 20 per cent of cases Chronic gastric ulcers vary greatly in size Alvarez and MacCarty[39] state that in a series of 638 simple chronic gastric ulcers 93 8 per cent measured less than 2 5 mm in diameter, the remaining 62 per cent ranging from 2 5 cms to 4 cms Duodenal ulcers are relatively smaller the larger lesions being found on the posterior wall

The chronic inflammatory reaction surrounding an ulcer may attain such pro portions as to form a large granulomatous tumor mass, similar in character and appearance to the extensive firmly indurated inflammatory masses which are found in the wall of the colon as a result of the progressive extension of a low grade inflammatory process from chronic diverticulitis In gross appearance such inflammatory masses may bear a very close resemblance to carcinoma, especially when the neighboring lymph nodes are enlarged

The tendency of fibroblastic tissue to contract results with great frequency, in certain deformities of the stomach and duodenum which profoundly affect the motor and secretory functions of the stomach The contraction of extensive cicatrices associated with large ulcers of the lesser curvature of the stomach, especially of the saddle back type may cause marked degrees of hour glass de formity of the stomach Far more often however such cicatricial contractures occur in the relatively narrow prepyloric part of the stomach and in the duodenum, causing varying degrees of stenosis and obstruction If of sufficient degree to interfere with the normal evacuation of chyme the scar tissue stenosis invariably will be found to be associated with an hypertrophy of the gastric musculature Cicatrical pyloric obstruction constitutes the most frequent complication of chronic peptic ulcer requiring surgical intervention

Jejunal ulcer subsequent to gastroenterostomy has the same pathological characteristics as gastric and duodenal ulcers The site may be at the stoma, form ing a gastrojejunal or marginal ulcer but more frequently is in the jejunum one half to one inch below the stoma Either afferent or efferent loop may be involved far more commonly the efferent The plastic exudate thrown out over the serosa at the base of the ulcer forms adhesions between the ulcer base and adjacent loops of small intestine or in many cases with the transverse colon Perforation of the ulcer may result in localized abscess formation or gastrocolic fistula

Symptoms

Epigastric distress is the most common symptom caused by gastric or duodenal ulcer the degree of discomfort varying from the mildest sensation of " indiges

tion" to pain of excruciating severity Peptic ulcer is not likely to be a very painful lesion in the acute and subacute phases of its development and both clinical and autopsy evidence indicates that chronic ulcer may exist without giving rise to subjective complaint The writer had under observation for some years a man with the typical cap deformity of duodenal ulcer who denied having any subjective distress but had recurrent massive hemorrhages It is quite certain that variable degrees of irritability of the sensory nervous system play an important role in the fluctuations in the intensity of the pain or discomfort caused by peptic ulcer An ulcer bearing individual may suffer severely while continuously engaged in some harassing occupation and gain a great measure of relief during a quiet, restful vacation

When such conditions exist as result in an ulcer producing discomfort or pain the distress usually occurs in such a characteristic manner that a highly probable diagnosis very often may be made from the history alone hence it is of the greatest importance that the precise facts particularly with regard to the time of occurrence of the distress be elicited clearly This may be done best by carefully questioning the patient as to the time of appearance of discomfort *in relation to* food taking during a usual day when three meals have been taken With rare exceptions the ulcer patient will be normally comfortable in the morning before breakfast when the stomach is empty No distress is experienced during breakfast or for at least an hour thereafter Frequently especially after a light breakfast *no distress will appear during the forenoon hours comfort continuing until* mid afternoon In the more painful ulcers however distress will occur between nine and eleven o clock mild at onset increasing in intensity and finally gradually disappearing prior to the mid day meal With delayed emptying of the stomach pain continues until food is taken with resulting immediate and complete relief The mid day meal is followed by a period of from one to three hours of comfort Usually by mid afternoon, however the ulcer sufferer is again aware of epigastric distress which in its crescendo rise in intensity almost invariably *becomes more* painful than the forenoon distress Again this either may disappear some time before the evening meal or may persist under the influence of abnormally long retention of food and acid secretion in the stomach until the evening meal when the ingestion of food again affords relief The evening hours may be free from pain if the ulcer bearer is at rest Ordinarily however distress recurs two or three hours after the *evening meal often with an intensity sufficient to prevent sleep* unless relief is obtained by taking some type of acid neutralizing agent such as bicarbonate of soda or a glass of milk

The characteristic relationship of peptic ulcer pain and distress to the digestive cycle is shown by an analysis of the records of 1 143 cases of gastric and duodenal ulcers reported by the writer[40] In this series distress was recorded as appearing

one to three hours after meals in 20 per cent, two to three hours after meals in 48 per cent and three to four hours after eating in 32 per cent No conclusions may safely be made as to the site of the lesion, whether gastric or duodenal, based on the time of appearance of pain

Pain awakening the patient between midnight and two A M nightly or for several nights during the week usually indicates the presence of an obstructive type of duodenal or prepyloric ulcer but this is not invariably true, since non obstructing gastric ulcer may be associated with a sufficiently marked degree of continued hypersecretion to cause severe nocturnal pain Duodenal ulcer and gastric ulcer located near the pylorus have a pronounced tendency to cause varying degrees of pyloric obstruction resulting in abnormally long retention of food and secretion in the stomach With very marked degrees of such an obstructive process food may be retained in the stomach from one day to the next The physiological effect of the continued presence of food in the stomach is manifested by a continuous secretion of gastric juice After a period of time the secretory glands, habituated to constant functioning continue to secrete large quantities of gastric juice even when the normal stimulus to secretion is lacking, namely, when no food is ingested

The occurrence of pain in the night hours possesses a high degree of significance as an index of pyloric obstruction and continued secretion, and when present as a feature of the clinical picture, is of prime diagnostic importance As a rule, the night pain of peptic ulcer is more severe than pain or distress present during the daytime and often results in either spontaneous or induced vomiting of highly acid gastric contents relief being obtained by emptying the stomach If the patient does not vomit recourse is apt to be had to the relief from pain which may be obtained from the acid neutralizing effects of milk, magnesia or bicarbonate of soda In the presence of a high grade continued secretion the relief obtained by these measures may last only a hour or two and the patient may be reawakened at intervals throughout the night each time gaining temporary relief by taking soda or milk Even without vomiting or resorting to neutralizing agents the pain may subside gradually in from one half hour to two or three hours, indicating a gradual emptying by the stomach of retained food and secretion

Emphasis must again be placed upon the fact that peptic ulcer is not necessarily a painful malady A survey of the clinical histories of 1,200 cases shows that 49 per cent of the patients described their subjective epigastric sensation as discomfort or distress and 51 per cent made the complaint of actual pain Characteristic of the life history of peptic ulcer are the remissions of symptoms resulting from greater care of diet the easing of nervous stress and strain or occurring, as is so often the case without recognizable cause

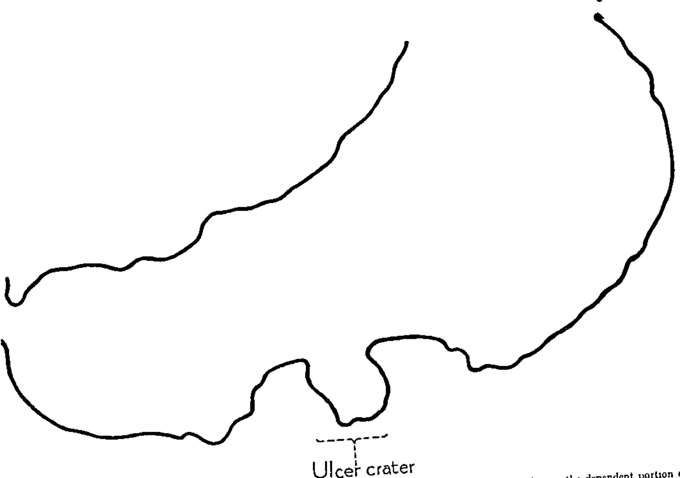


Fig 2 Mr S H age 52 Exact reproduction of the contour of an x ray film of a large gastric ulcer in the dependent portion of the greater curvature which was resected and proved histologically to be benign This is the only case of benign gastric ulcer in this area the writer has ever observed

Distress or Pain

The most characteristic feature of ulcer pain or distress other than its time relationship to food taking is its sharply defined localization in the epigastrium With rare exceptions an individual having an active ulcer will indicate the site of pain by unerringly placing the tip of one or more fingers precisely on a sharply circumscribed spot which in a given person invariably will be constant In no other type of abdominal pathology is this definite localization of pain so strikingly a feature of the clinical picture Rarely the site of pain will be in the gall bladder region or behind the lower third of the sternum Radiation of pain to the lower dorsal region is common in posterior wall duodenal ulcer which has involved the pancreas and very high posterior wall gastric ulcer may cause pain in the left supraclavicular area by involvement of the left diaphragm (Fig 3)

The ulcer patient often has difficulty in finding the right word to describe his distress, especially if it is relatively mild More pronouced types of distress and pain will be described in the order of frequency as gnawing dull aching burning, boring or rarely cramp like Associated with various types and degrees of distress may be mild nausea or a sensation of epigastric depression or "goneness"

Divergent views have been expressed regarding the production of ulcer pain, but there can be no doubt of the fact that it is caused by the action of free hydrochloric acid on the surface of the ulcer Experimental evidence has been supplied by Palmer[4] who introduced a solution of 0 5 per cent HCl into the stomach of patients with gastric and duodenal ulcer, producing distress, identified by the patient as typical in 95 per cent of the tests Pain could be produced and relieved at will by the introduction and withdrawal of physiological concentrations of HCl In Palmer s experiments the relationship between the concentration of the acid and the severity of the pain seemed at times to be almost a quantitative one He concluded that the variable factors in the production severity and duration of ulcer pain include the following (1) the sensitiveness of the pain producing mechanism (2) the concentration of the acid (3) the amount of acid (4) the duration of time of exposure of the ulcer surface to acid (5) the emptying rate of the stomach and (6) the rate and amount of duodenal regurgitation of bile and pancreatic juice A somewhat bizarre bit of clinical evidence seems worth recording The writer has observed 2 cases of jejunal ulcer in which with clock like regularity two hours after each meal pain gradually increasing to great severity would occur in the left testicle This testicular pain could be relieved invariably and immediately by giving the patient a glass of milk or an alkaline powder In each case a deeply penetrating jejunal ulcer was surrounded by an inflammatory mass which extended far into the left abdomen evidently involving the renal nerve supply

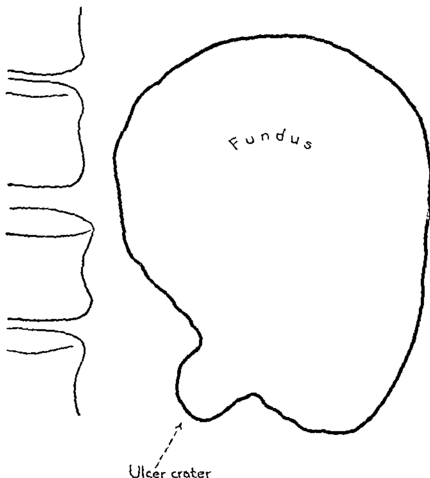


Fig 3 No 1 Mr C C age 55 This x ray film contour was made with head of fluoroscopic table depressed so that all barium in the stomach completely fills the fundus and upper third of the stomach also with the patient lying on his side (note relation of barium mass to the spine) *In this manner is clearly visualized the extent of the ulcer crater high on the posterior wall of the stomach*

The quantity and quality of food usually influences the distress in a manner sufficiently characteristic to be of value in diagnosis Salads radishes uncooked cabbage pickles, raw fruits, nuts and other similar items of diet which are apt to be ingested in a coarsely subdivided form cause increased distress not so much by mechanical irritation of the ulcer as by causing delay in the emptying time of the stomach and prolongation of the influence of the acid irritant factor Con

versely cooked cereals milk, soft eggs, baked and mashed potatoes, vegetable purees, custards and similar bland foods are likely to lessen greatly the amount of discomfort experienced A meal rich in albuminous foods will be followed invariably by a longer period of comfort than one containing a minimum of acid binding proteins Ulcer pain may appear within 30 minutes after a lunch of clear soup salad coffee and fruit In general the larger the meal the longer will the onset of distress be postponed

The direct relationship between the pain of ulcer and the presence in the stomach of uncombined hydrochloric acid is shown by the manner in which ulcer distress is relieved regularly and almost immediately by the giving of an alkali in amount sufficient to neutralize completely or to lower greatly the concentration of the free hydrochloric acid invariably associated with ulcer pain Epigastric distress due to uncomplicated peptic ulcer will be relieved in from one to five minutes by the administration of 4 gm (1 ʒ) of calcium carbonate A glass of milk is equally effective Sodium bicarbonate is less useful as a test powder, due to the large volume of carbonic acid gas liberated By over distending the stomach this may cause so much discomfort as to make a correct interpretation of the test difficult If a given epigastric pain or distress is uninfluenced by these acid neutralizing agents, the cause of the distress should be sought in some disorder other than peptic ulcer

Local Tenderness

The presence of a sharply circumscribed (finger point) area of tenderness is the most important physical sign in the diagnosis of peptic ulcer Most commonly this point of tenderness is situated in the right epigastrium over the right rectus muscle and muscle resistance to palpation of this area is apt to be present in varying degrees notably when spontaneous pain is at its height Marked degrees of local tenderness and rigidity indicate extension of the inflammatory process to the peritoneum It must be remembered that in many individuals especially when reclining a large portion of the stomach lies above the level of the costal margin Thus large and deeply penetrating ulcers of the lesser curvature and posterior wall may exist in areas inaccessible to palpation It may also be difficult to discover local tenderness in duodenal ulcer in the broad chested sthenic type of individual with transversely situated high lying stomach In such cases the first portion of the duodenum may be too inaccessible for effective palpation Particular emphasis must be placed upon the fact that local tenderness invariably will be found most readily at a time when the patient is having distress

Jejunal ulcer is commonly associated with very definite local tenderness usually well to the left of the midline although the site will vary dependent upon the

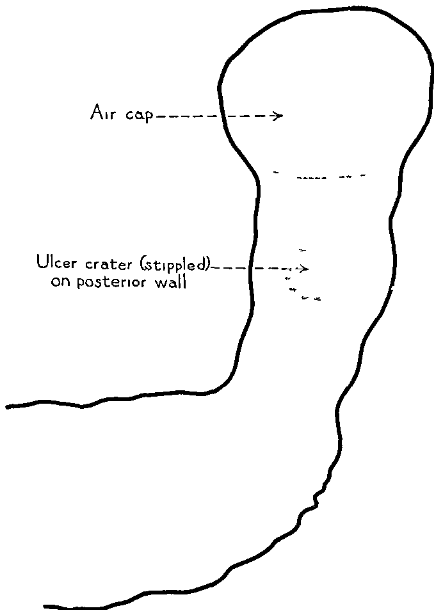


Fig 3 No 2 Schematic sketch of x ray film of same pat ent shown in Fig 3 No 1 made with patient in upright po ture The perigastric nflammatory ma s about the base of this ulcer involved the under surface of the diaphragm and thus caused pain in the left upraclavicular region occurring with clocklike regularity night after night at mid ni ht and relieved immediatelv by sodium bicarbonate a mo t unusual localization of ulcer pain This lesion healed readily

position of the gastroenterostomy stoma For this reason palpation is most informative when made under the fluoroscopic screen

Vomiting

Vomiting is not a particularly common symptom in ulcer When a prominent feature of the clinical picture usually it is due to some degree of temporary or permanent pyloric obstruction causing retention of gastric contents into the night hours However vomiting may occur in non obstructive ulcer in susceptible individuals who develop nausea as ulcer pain increases in intensity, culminating in vomiting as the pain reaches its height In patients with a marked degree of pyloric obstruction the stomach becomes distended with retained food and fluids during the late afternoon and evening, causing such a degree of discomfort as to result eventually in either spontaneous or induced vomiting This may be delayed until midnight or later when more or less severe ulcer pain is apt to be a part of the picture Emesis then is likely to yield large volumes often a liter or more, of highly acid gastric contents chiefly fluid containing food elements ingested 12 to 24 or more hours earlier Microscopic examination may reveal the presence of sarcinae and yeast a finding pathognomonic of pyloric obstruction of such degree as to cause continuous retention of food in the stomach

Hemorrhage

It is probable that some slight amount of hemorrhage occurs during the acute phase of every peptic ulcer and a large proportion of patients with chronic ulcer have occult blood in the feces on a hemoglobin free diet when first observed clinically Fortunately in the majority of cases such bleeding as occurs is too insignificant to influence appreciably the health of the individual, amounting merely to slight oozing However serious degrees of loss of blood occur with such frequency and dramatic suddenness as to place massive hemorrhage in the fore front of the grave complications of gastric duodenal and jejunal ulcer In a series of 1 224 cases of ulcer reported by the writer in which the status of the cases was obtained by personal interview or by letter from 2½ to 15 years after medical treatment for ulcer at the Presbyterian Hospital it was found that 19 per cent gave a history of having had one or more massive hemorrhages prior to admission to the medical service, and 5 per cent had hemorrhage subsequently forming an impressive total of 24 per cent of these patients who at some time during the course of the disease had gross hemorrhage

Gross hemorrhage occurs without warning Commonly the patient suddenly experiences a sensation of great weakness and faintness associated with some de

gree of nausea and frequently vertigo The skin becomes cool pale and covered with cold perspiration Syncope may or may not occur depending upon the rapidity and extent of loss of blood, but is very common The radial pulse becomes small in volume and vomiting often occurs at this initial stage If hemorrhage continues the patient becomes anxious restless very pale and thirsty and unless emergency measures are carried out speedily air hunger type of respiration may develop and the blood pressure may fall to such a degree that the radial pulse becomes almost impalpable Death may occur at this time but as a rule the profound fall in blood pressure facilitates coagulation of blood at the bleeding point and hemorrhage either ceases or is reduced markedly in volume Subsequently the thrombus may be either dislodged or digested by gastric juice, like any other albuminous substance with recurrence of hemorrhage Death occurs more commonly in one of these subsequent hemorrhages than in the primary one Instead of successive hemorrhages over a period of two three or more days the blood loss may be continuous to the point of exsanguination

Death is far less likely to occur in the young or in individuals of middle age who are relatively free from arteriosclerosis than in those usually older who have sclerosed arteries The majority of deaths in ulcer hemorrhage is observed in patients in whom the eroded artery is found to be atheromatous to such a degree as to be incapable of contracting

Massive hemorrhage may manifest itself either in the form of hemetemesis or melena and this holds true irrespective of the site of the ulcer whether gastric, duodenal or jejunal The lesion may be in the jejunum in some of the most desperate cases of hemetemesis If the hemorrhage is due to erosion of a vessel of considerable size permitting the rapid loss of a great volume of blood it is likely to be vomited at once as bright red blood If the bleeding is of a less critical character, considerable quantities of blood may accumulate in the stomach and coagulate into dark red liver like masses prior to being vomited Smaller amounts of blood may remain in the stomach long enough to permit of the oxidation of hemoglobin so that when emesis occurs the blood has the appearance of coffee grounds

A review of the case histories of 202 cases of gross hemorrhage shows that in this series hemetemesis of some degree with coincident or subsequent melena occurred in 54 per cent, and that blood was evacuated only through the intestine in 46 per cent of these cases *As a rule in gross hemorrhage the feces have a characteristic tarry appearance* but it is not uncommon for dark red liquid blood to be passed by bowel in critically severe cases The number volume and character of the stools passed during the first two or three days after the initial symptoms of hemorrhage supply valuable information as to the status of the patient during this period Frequent and copious liquid stools black or dark red in color indi

cate active continuation of hemorrhage Conversely, absence of bowel movements is an excellent prognostic sign The first highly probably evidence of cessation of hemorrhage is the appearance of a light colored stool

A not infrequent form of hemorrhage is that in which, without a gross hemorrhage episode a steady, slow oozing of blood continues for weeks or possibly months blood being passed continuously in the feces, possibly in amounts too small to influence the color of the stools thus failing to attract attention Hemorrhage of this type is far more common in duodenal than in gastric ulcer and may cause profound anemia It must be remembered that the discomfort caused by chronic peptic ulcer may be of the mildest character Also there is little relationship between the degree of painfulness of ulcer and its tendency to hemorrhage Hence the necessity for careful examination of the feces for occult blood in all cases of unexplained anemia The differential diagnosis of the various causes of hemetemesis and melena are discussed in a subsequent section

Loss of Weight

The body weight usually is well maintained, the exceptions falling within two groups Very painful types of ulcer frequently are associated with loss in weight resulting from an inadequate food intake the patient avoiding eating in an effort to lessen the amount of pain High degrees of pyloric obstruction or obstruction due to hour glass deformity of the stomach often result in emaciation due to vomiting of a large part of the food ingested

Appetite

The appetite rarely is impaired except in cases of pyloric obstruction of such degree as to cause pronounced food stagnation Even in these cases patients may take breakfast and possibly the mid day meal with excellent relish but will have no desire for the evening meal the stomach then being more or less distended with retained food and secretion Not infrequently the ulcer sufferer will set forward the time for food taking in order to secure relief from what he concludes to be ' hunger pain The keen desire for food of the average ulcer patient is in marked contrast to the anorexia of gastric cancer

Analysis of Stomach Contents

Information regarding the secretory function of the stomach is essential to proper diagnosis and treatment of peptic ulcer and its complications The fractional method should be used whenever it is necessary to record the acid values

at all levels of the acid curve and should be supplemented by histamine in cases of very low free HCl, but the simple Ewald test meal supplies sufficiently accurate information for practical clinical purposes in the great majority of ulcer patients This te t meal consists of 60 gm of white bread and 300 c c of water given when the stomach is empty preferably in the morning The gastric content is aspirated and titrated one hour later From the figures in a Presbyterian Hospital series of cases (Table I) the following information on free HCl acidity in peptic ulcer is obtained

TABLE I

GASTRIC ACIDITY IN 1 224 CASES OF PEPTIC ULCER

Number of cases with free hydrochloric acid between	
1 and 20	33
0 and 30	87
30 and 40	180
40 nd 50	2 8
50 and 60	250
60 and 70	210
70 and 80	120
80 and higher	75
No record	33

Hyperchlorhydria is present in 75 per cent of cases the free HCl ranging between 40 and 90 clinical units In 22 per cent of cases the acidity is within the limits usually accepted as normal namely free HCl between 20 and 40 In only 3 per cent of cases are subnormal acid values found In general acidity is higher in duodenal than in gastric ulcer but gastric ulcer often is associated with very high acidity especially when the lesion is large and of long duration so that no special significance is to be found in this difference

The writer has never seen an ulcer case with total achlorhydria namely with no free HCl in the gastric content under stimulation by histamine A peptic ulcer cannot form in the stomach or duodenum in the absence of gastric juice secretion The chronic stages of ulcer may however be associated with a diffu e chronic gastritis which may lead to the gradual lowering of the secretion of gastric juice In rare instances this suppression of the secretory function of the gastric glands in an ulcer bearing stomach with gastritis may reach a point where only minimum amounts of hydrochloric acid are present but such cases are extraordinarily uncommon

Motor Function — Delayed emptying time of the stomach is so common a feature of obstructive duodenal ulcer and of juxtapyloric gastric ulcer that a knowledge of the motor function is desirable This may be obtained by giving a full rather coarse meal containing among other items meat cooked vegetables

salad vegetables and uncooked fruit Following such a meal the stomach normally will be empty within 4 or 5 hours Any appreciable quantity of food removed from the stomach by the tube 7 hours after the ingestion of a motor meal may be considered evidence of a motor insufficiency Food stasis may occur due to causes wholly apart from pyloric obstruction Psychic influences fear, grief and nausea from any cause may markedly depress peristaltic activity and lead to abnormal retention of food in the stomach

Occult Blood — Relatively little value attaches to the examination of gastric contents for occult blood in peptic ulcer Material obtained by the tube often contains minute amounts of blood due to traumatism of the mucosa by the tube Specimens of vomitus have greater value for this purpose, and strong occult blood reactions in vomited material may be used with caution as an aid in the diagnosis of gastric pathology Negative tests for occult blood in the stomach contents should never be considered a reason for excluding ulcer

Microscopic Analysis — The finding of sarcinae or yeasts in abundance is proof positive of the over night retention of food in the stomach for a period of at least many days and is an index of pyloric obstruction of high degree Failure to find sarcinae under such conditions may be explained if the patient has been using bicarbonate of soda for relief of ulcer distress, as this salt inhibits the growth of sarcinae

Examination of Feces

In the absence of recent gross hemorrhage untreated chronic peptic ulcer often but not uniformly will cause occult blood in the feces hence failure to find occult blood cannot be used as evidence to exclude ulcer Routine daily stool examinations especially during the first two weeks of treatment, are of great value especially in the hemorrhagic type of ulcer the gradual disappearance of occult blood being the most useful index of the progress of the case Conversely, if 3+ to 4+ occult blood reactions continue to be found in the feces after a reasonable period of treatment the case should be reviewed in a critical manner Usually some error in management will be disclosed such as failure to deal with a previously unrecognized continued nocturnal hypersecretion Occult blood tests are also of vital importance during the early weeks of treatment of gastric ulcer, since it is one of the means of differentiating a simple benign ulcer from carcinoma Gastric carcinoma almost invariably causes continuous and strongly positive occult blood reactions in the stools One should never be content with the progress of any case of gastric or duodenal ulcer under medical treatment, if occult blood persists in the stools for longer than 10 days to 2 weeks after placing the patient on effective management

Blood Changes

Peptic ulcer causes no characteristic changes in the blood In the absence of hemorrhage or a marked degree of malnutrition the blood picture usually is normal or approximately so Immediately after a severe hemorrhage there is likely to be a lowered blood volume for 1 to 3 days hence the true degree of anemia is not likely to be reflected accurately by the initial blood count but rather by the counts made on about the third day, by which time there will have been opportunity *to restore a more normal blood volume through absorption of fluids*

A low grade fever, accompanied by a moderate leukocytosis usually may be observed the day after a moderately severe hemorrhage declining to normal after 3 or 4 days

Diagnosis

Peptic ulcer has long since ceased to be an obscure disease The great frequency of its incidence and the serious economic losses caused thereby the threat to life inherent in perforation and recurrent episodes of massive hemorrhage and the necessity so often arising for major surgery have combined with an exceeding̃ly voluminous literature made both physician and layman ulcer conscious Notwithstanding this fact however, in only a small fraction of ulcer sufferers is the lesion recognized and treated at a time when treatment of the ulcer and regulation of the life and habits of the patient would be most effective especially in preventing recurrences and avoiding the pathological sequences in the life history of chronic peptic ulcer which all too often makes surgery imperative Peptic ulcer does not commonly present a difficult problem in diagnosis This is due in large part to the clear cut characteristics of ulcer distress to the invaluable evidence derived from physical examination and to simple tests of the gastric function as well as to the excellence of modern x ray technique

The initial approach to the diagnosis of peptic ulcer should be based upon recognition of the fact that the distress or pain of ulcer is directly related to the coincident presence in the stomach of uncombined HCl in amount and concentration sufficient to cause discomfort In other words the distress or pain of ulcer when ulcer is causing subjective discomfort occurs with definite relationship to food taking during a certain period of the digestive cycle Furthermore under the *digestive conditions associated with the taking of three ordinary meals* daily the time interval between the meal and the onset of distress is apt to be in a given individual strikingly constant from day to day and from week to week Repeatedly the statement is made by ulcer patients with regular habits of eating that a clock might be set by the regularity in time of appearance of their discomfort A corollary fact of some importance in diagnosis is that the distress symp-

toms of ulcer are typically periodical in appearance often with periods of weeks or months of freedom from distress between attacks, but during a given p riod of existing discomfort the patient usually experiences distress at some stated time during the day either regularly day after day or at least during most days of the week

The following facts are useful in diagnosis (1) the distress of ulcer is absent when the stomach is empty namely, when the stomach contains only the normal amount of fasting stomach secretion (2) it never appears during food taking (3) it appears after an appreciable interval usually 2 to 3 hours, after eating (4) it is relieved invariably by food taking provided the meal taken contains an average amount of albuminous food (5) it is relieved by alkalis (6) the distress is associated with the presence in the stomach of a free hydrochloric acid content in quantity exceeding the normal fasting secretion (7) it is sharply localized and (8) it is relieved by emptying the stomach with the tube or by vomiting In a given case under observation for diagnosis a distress, that does not test out in conformity with these clinical facts is not likely to be due to peptic ulcer It is probable that in no other malady does the time and skill devoted to securing an accurate history yield information of such determining diagnostic value as in peptic ulcer The current tendency to place chief reliance for the diagnosis upon x ray examination rather than upon thorough clinical study is unfortunate

Merely to determine the presence of ulcer is by no means sufficient for a working diagnosis Knowledge in a given case of one or more of the possible complications is not only essential to an understanding of the clinical manifestations of the disease but is a necessary prerequisite to rational treatment Investigation should be made in each case for evidence of the following complications

(a) *Pyloric obstruction* due to cicatricial narrowing to inflammatory swelling and edema of the tissues about the ulcer and to spasm of the pyloric sphincter and adjacent segments of the stomach and duodenum Frequently all three of these obstructive factors are present in varying degrees and it is necessary to differentiate clearly between the causes for obstruction which are readily relievable by medical treatment namely spasm and inflammatory swelling and the fixed stenosis of an unyielding cicatrix

(b) *Excessive Continued Secretion of Gastric Juice*,

(c) *Perigastritis and Periduodenitis*

(d) *Hour glass Deformity of the Stomach*

(e) *Perforation*

(f) *Hemorrhage*

After careful verification of the facts in the history a detailed physical examination should be made particular care being taken to investigate any suspected

focus of infection about the teeth or in the tonsils or nasal sinuses as well as any signs of anemia or evidence of malnutrition Palpation of the upper abdomen should be done with especial care and insofar as possible with the stomach empty The finding of a single isolated point of exquisite tenderness on deep palpation in conjunction with a history of epigastric distress occurring 2 or 3 hours after meals and relieved by food taking or soda justifies the highly probable diagnosis of active peptic ulcer Chronic indurative types of ulcer especially when located near the pylorus, will be surrounded occasionally by a palpable inflammatory mass of such size and consistency as to suggest carcinoma Visible peristaltic waves constitute a physical sign of primary importance in the diagnosis of pyloric obstruction as will be made clear in a subsequent paragraph Succussion sounds yield evidence suggestive of pyloric obstruction

The diagnostic evidence obtained from the history and physical examination should be supplemented as soon as possible by a test of the secretory function of the stomach providing there exists no contraindication to the use of the tube such as recent massive hemorrhage aortic aneurysm very marked arterial hypertension advanced pregnancy or advanced age of the patient If an Ewald test meal yields no free hydrochloric acid or subnormal free HCl values a fractional test meal should be given as a somewhat more exact test of the secretory function If no HCl is found the test should be repeated supplemented with an injection of histamine A further useful test of the secretory function is that of an ordinary full meal with aspiration two and one half hours later namely at approximately the height of the secretory curve Failure to carry out such tests of the gastric secretory function may result in errors in diagnosis The writer once made such an error in this case a fatal one A woman aged 50 who had an ulcer history and a very large lesion of the posterior wall at the junction of the middle and distal thirds of the stomach had no free HCl by Ewald test Carcinoma was diagnosed and gastric resection was done She succumbed from the operation The pathological lesion was that of a very large benign gastric ulcer Had further tests of of the secretory function been made and the free HCl which was almost certainly present been found a brief period of ulcer management might well have resulted in establishing a correct diagnosis and recovery of the patient

Subnormal acid values will be found rarely in cases of duodenal ulcer but are not uncommon in gastric ulcer a fact of some importance in the differential diagnosis between benign and malignant lesions

Since the presence of occult blood in the feces may be of determining value in the diagnosis it is well to place the patient on a meat free diet at once as 3 days should elapse before occult blood tests may be accepted as valid evidence of pathology

It is desirable to obtain all the evidence possible to be derived from the his-

tory and physical examination and, if time permits, from the chemical tests as well before the x ray study is made By so doing not only is it usually possible to make a very probable tentative diagnosis but the information brought by the clinician to the aid of the x ray study gives invaluable direction to the hand and eye of the examining roentgenologist and makes for a degree of thoroughness of search that leaves few ulcer lesions unvisualized when the examination is made by a skilled radiologist

When the diagnosis is in doubt, the patient should be kept under observation and if possible hospitalized with a view of determining whether the manner of occurrence of distress or pain is actually as described in the recorded history, and whether the distress appears and disappears under conditions consistent with the distress of ulcer The patient is placed upon a rather coarse type of diet, designed to accentuate the symptoms and is kept ambulatory The time of appearance of discomfort in relation to meals is noted and the effect upon the distress of food, appropriate amount of alkalis and emptying the stomach by the tube is observed The stomach is aspirated at the height of distress to ascertain whether or not a free hydrochloric acid content adequate to cause ulcer discomfort is present, and whether or not the removal of the acid irritant results in complete relief If such a period of observation and testing of a suspect ulcer patient yields evidence entirely consistent with the known characteristics of ulcer distress, one is justified in placing the patient tentatively upon medical treatment for ulcer as an ulcer suspect even though the x ray examination has been inconclusive It must be made clear, however that if the clinical testing of a suspect ulcer distress in this manner shows a single definite incompatibility to the ulcer type, such for instance as when the patient s characteristic pain continues throughout and after an ordinary meal or fails to be relieved by a suitable dose of alkali, a diagnosis of ulcer is not permissible

Radiological Evidence

The present day technical excellence of x ray examination of the digestive tract has made it an indispensable aid in the diagnosis of peptic ulcer So very useful is it, in fact that there is an unfortunate tendency to rely almost solely upon x ray findings for the diagnosis of gastric and duodenal ulcer rather than upon thorough clinical study This is to be deprecated for several reasons, not the least being the value to the radiologist of an accurate summary of the significant facts in the case he is to examine

An empty stomach is absolutely essential to successful fluoroscopy hence the examination should be made in the morning the patient having been given nothing by mouth since the previous evening In cases of pyloric obstruction the stomach should be lavaged at bedtime and immediately before the x ray examination the

following morning it should be aspirated again to remove any continued secretion present

The fluoroscope is more generally valuable than serial films in the visualization of ulcer, especially in the detection of gastric ulcer and small crater type ulcers of the posterior wall of the duodenum which are seen best upon manipulation of *the stomach or duodenum and with relatively small amounts of barium* Fortunately the majority of gastric ulcers are located either on the lesser curvature or in close proximity to it where they can be visualized readily The patient should be slowly rotated to right and to left to bring into view every contour of the anterior and posterior walls Direct evidence consists in the visualization of a crater or of a deformity in the contour of the stomach or duodenum considered characteristic of ulcer

The typical x ray appearance of gastric ulcer is that of a niche projecting from the lesser curvature of the stomach in any segment from cardia to pylorus but most frequently in the middle third In size the niche may vary from a barely discernible papule like shadow to the very extensive defects caused by large deeply penetrating ulcer *Such a cone shaped shadow projecting from the lesser curvature* may be 3 centimeters or more in depth and 3 to 3½ centimeters in width at the base The niche may be so large that with the patient in an erect position barium may be retained in the ulcer crater when the adjacent segment of the stomach is free from barium with an air bubble visible above the barium level in the crater Such defects invariably are found by palpation to be fixed in position Varying degrees of spastic or cicatricial hour glass contraction of the stomach often are associated with lesser curvature lesions

Ulcers situated near the cardia or in the posterior wall of the fundus may escape detection unless a certain technic is employed *The area referred to must* be inspected minutely during and subsequent to the swallowing of only a small portion of barium solution routinely two mouthfuls In this way any irregularity in the parallel arrangement of the rugae may be seen (stellate arrangement in ulcer) and small penetrating ulcer defects can be visualized that are completely obscured when the stomach is filled with a contrast medium Penetrating ulcers high on the posterior wall are seen best by rotating the patient in a recumbent position and with the head of the fluoroscopic table depressed (Fig 3) Visualization of the fleck of barium which is evidence of the presence of a small crater ulcer of the posterior wall of the stomach or duodenum is accomplished by skillful manipulation either with the hand or by the use of a pressure cone using preferably only a small amount of barium If an ulcer of this type is present it will be found upon carefully expressing barium from the area with the examining hand The portion of barium filling the crater remains fixed in one spot and cannot be wiped out by pressure thus being readily detected

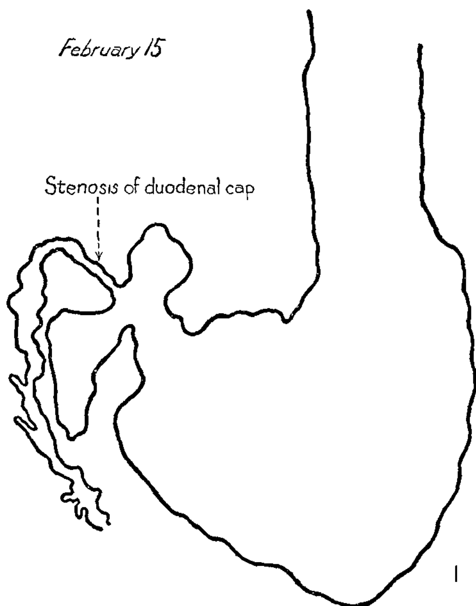


Fig 4 No 1 Mrs E C age 36 X ray film contour of ob tructive type of duo denal ulcer of 2 years duration with typical epigastric distress night pain, nausea vomit ing weight lo s of 15 pounds and recent severe hematemesis Bedtime aspiration volume 250 c c to 300 c c Note marked degree of enosis of duodenal cap

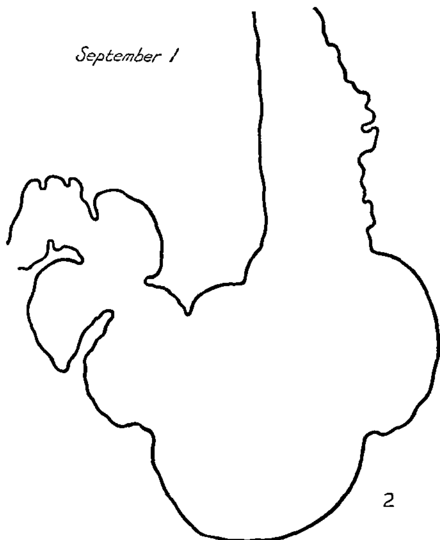


FIG 4 No 2 This shows restoration of good lumen after disappearance of inflammatory swelling and spasm in the patient described in the legend of Fig 4 No 1 Ulcer healed. Normal emptying of stomach No recurrence during 9 years

Duodenal ulcer unless very superficial usually causes varying degrees of deformity of the contour of the duodenal bulb due to spasm inflammatory tumefaction and cicatricial contraction As a rule all three factors are present in greater or lesser degree especially in an ulcer of considerable chronicity In ulcer

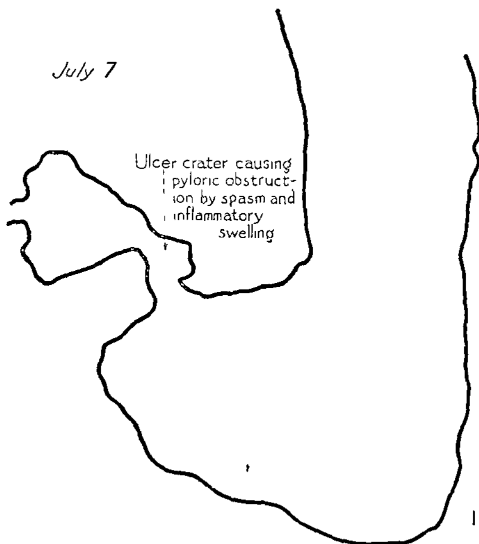


FIG 5 No 1 Mr A I age 47 Crater ulcer in antrum which was roentgenologically diagnosed carcinoma causing pyloric obstruction A diagnosis of benign gastric ulcer was made as a result of the progressive disappearance of the crater of the obstruction and of occult blood in the stool under ulcer treatment

of more recent origin the deformity may be due almost entirely to spasm Small crater ulcers of the posterior wall may not cause any recognizable deformity in the contour of the cap and may easily escape detection unless the technique already mentioned is employed This is also true of small posterior wall ulcers in the antrum of the stomach Furthermore duodenal ulcer situated at the apex of the

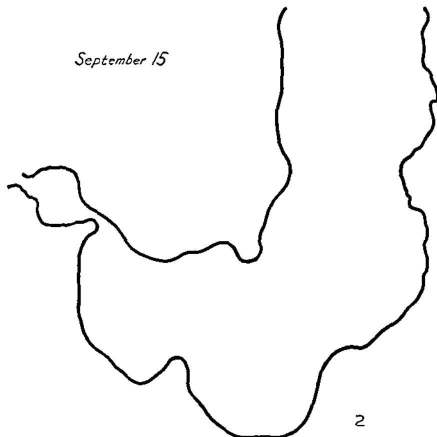


FIG 5 No 2 X ray of patient shown in Fig 5 No 1 checked 10 years later with no recurrence of gastric pathology in interim

cap especially in cases in which the duodenum turns downward from this point at a rather sharp angle are difficult to visualize and if the first portion of the duodenum curves markedly backward are not easily demonstrated in films Such ulcers often are of the obstructive type and thus there may be an unusually large well filled cap of normal contour except at the difficulty visualized apex It is particularly in dealing with this localization of ulcer that the radiologist requires some knowledge of the clinical picture in order to avoid an error in x ray diagnosis

Duodenal ulcer may not only cause spastic contraction of the wall of the duodenum at the site of the ulcer but to a marked degree of the adjacent pylorus and of the prepyloric area as well A deformity of the distal segment of the

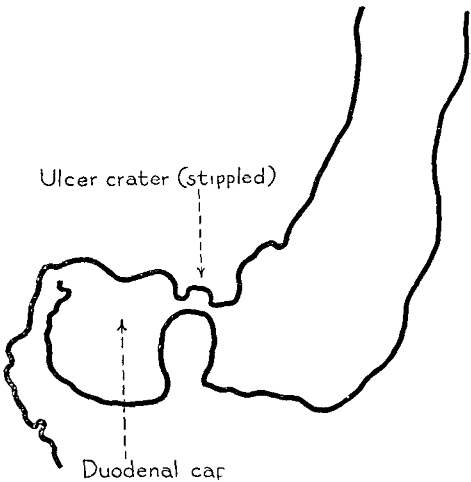


FIG 6 Mr S B age 55 X ray film contour showing crater type gastric ulcer in the pylorus with hour glass deformity History of epigastric distress relieved by sodium bicarbonate intermittent for 6 years during which time patient had had several brief periods of medical treatment Free HCl 54 total acidity 96 The stomach emptied normally through the narrowed pylorus All stools were negative for occult blood during a period of 2 weeks of hospital observation

stomach thus produced is a not infrequent source of error in diagnosis as it may simulate the appearance of a small carcinoma

The caliber of the stream of barium passing through the markedly deformed cap in cases of chronic duodenal ulcer may be so very small as to indicate an extreme degree of stenosis In all such cases it must be borne in mind that obstructive factors relievable by treatment namely spasm and inflammatory swelling are present in some degree if the ulcer is active and that the actual amount of per

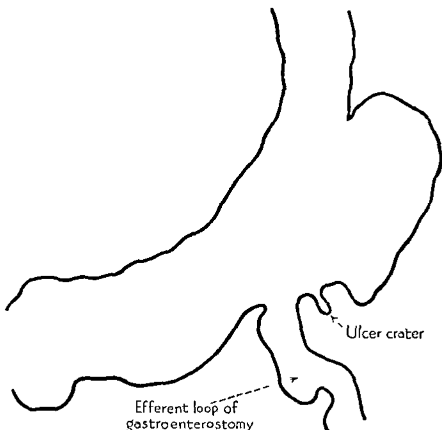


FIG Mrs A B age 38 \ ray contour of film of gastrojejunal ulcer \ote "tucking up of lower border of stomach in area adjacent to the ga troentero tomy stoma which cannot be seen The fferent loop also is not seen

manent scar tissue contraction can be determined fluoroscopically only by re examining the patient after a period of effective ulcer treatment (Fig 4)

The distinction between a healed and an active duodenal ulcer is based upon the presence or absence of pasm causing irritability of the musculature of the duodenal bulb Ordinarily the degree of spasm and irritability is in direct pro portion to the activity of the ulcer Local tenderness will be a feature of untreated active ulcer but the inflammation surrounding an ulcer subsides under bed rest and ulcer treatment and the roentgenologist may find no local tenderness in a treated ulcer which is still far from being healed

Peptic ulcer located in the antrum of the stomach may produce extensive filling

defects indistinguishable from the filling defects caused by carcinoma The writer has seen repeatedly an x ray diagnosis of gastric carcinoma made in cases where it was possible to prove by clinical evidence that the existing lesion was a wholly benign peptic ulcer with extensive surrounding inflammatory tumefaction Such cases, by no means uncommon clearly illustrate the necessity for accurate, clinical diagnostic study prior to as well as subsequent to, x ray examination Certainly there is a very definite proportion of prepyloric lesions in which the differential diagnosis between simple gastric ulcer and carcinoma cannot be made by the x ray alone (Figs 5 and 6)

Indirect evidence of the possible presence of ulcer may be obtained by observing certain variations from the normal Thus an increase in the number and depth of gastric peristaltic contractions suggests a lesion at or near the pylorus causing some degree of obstruction especially if associated with delay in the passage of barium through the pylorus Abnormally long retention in the stomach of a barium meal may be due to pyloric obstruction, but in general this method of determining the motor function is less accurate than the use of a full course meal in the manner described It must not be forgotten that gastric motility may be completely inhibited by nausea and especially by the fear and anxiety so likely to be present in an apprehensive patient undergoing fluoroscopic examination The examination will be greatly facilitated in such instances by gentle handling and a reassuring word When obstruction results in retention, the antrum dilates, and eventually the entire stomach may become markedly hypotonic Failure of peristaltic waves to pass through a given area of the stomach wall in a normal manner is presumptive evidence of some infiltrative lesion Also any distortion of the normal rugae pattern in any area in the stomach suggests either an active or a healed pathological process and while usually due to peptic ulcer may be caused by a small scirrhus carcinoma A sign of definite value is the shortening of the lesser curvature contour with tucking up ' of the distal third due to tonic spasm of the longitudinal muscles caused by an ulcer on or near the lesser curvature A persistent spastic incisura of the greater curvature may lead to the detection of a lesser curvature ulcer Spasm and abnormally rapid emptying of the duodenal bulb is suggestive of a pathological lesion in this area Great caution should be exercised however in diagnosing gastric or duodenal ulcer on indirect evidence alone

Jejunal Ulcer — The characteristic fluoroscopic finding in marginal or jejunal ulcer is a persisting fleck of barium in the ulcer crater visualized by careful manipulation of the area about the gastroenterostomy stoma Since the great majority of gastroenterostomies are done posteriorly the detection of these ulcers which as a rule have relatively small craters requires the exercise of both patience and skill An associated sign of great value is the tucking up of the stomach wall

immediately adjacent to the stoma (Fig 7) Also, any evidence of stenosis of the stoma or of either the afferent or efferent loops of jejunum within a range of 2 or 3 centimeters below the stoma is indicative of ulcer If a jejunal ulcer is seen the possibility of a fistulous communication with the colon should be kept in mind Marginal and jejunal ulcers usually are associated with definite tenderness on palpation and frequently with a palpable mass as well both findings being discovered more readily under the fluoroscope than during routine physical examination

A barium meal should never be given without the subsequent administration of mineral oil or the use of such other means as may be deemed most suitable to insure proper evacuation of the barium Failure to observe this precaution not only causes acute discomfort due to severe obstipation but may have more serious results The writer observed a case of acute intestinal obstruction requiring surgical relief from the lodging of barium in diverticulae of the sigmoid and an ensuing acute diverticulitis

Diagnosis of the Complications

Pyloric obstruction may be considered the most common complication of peptic ulcer An impression of its frequency may be gained from the writer s study of 1 224 cases of ulcer In this group no less than 425 patients 34 per cent complained of being wakened from sleep by pain during the night hours a symptom usually caused by delayed emptying time resulting from pyloric obstruction Obstruction to the passage of food through the outlet of the stomach of some degree may be said to exist when it is necessary for the stomach musculature to exert greater than normal effort to expel the chyme into the duodenum If such an obstruction persists for a considerable period of time the gastric musculature hypertrophies to so marked a degree that the powerful muscular contractions of the stomach affect the contour of the abdominal wall and wave like changes in contour of the epigastrium moving slowly from left to right may be seen Visible gastric peristalsis in an individual with an abdominal wall of normal thickness and normal muscle tone constitutes a physical sign pathognomonic of obstruction

Evidence of pyloric obstruction should be sought when any of the following symptoms or signs are present (a) pain disturbing sleep between midnight and the early hours of the morning this will be due usually but not invariably to an *outlet ulcer with obstruction occasionally a large gastric ulcer far removed from* the pylorus may give rise to continued hypersecretion and severe nocturnal pain (b) recurrent vomiting of food eaten twelve hours or more prior when other more transient causes for food stasis such as the nausea of migraine have been excluded (c) vomiting of greater quantities of material than have been taken into the stomach the vomitus consisting largely of fluid having a very sour taste and

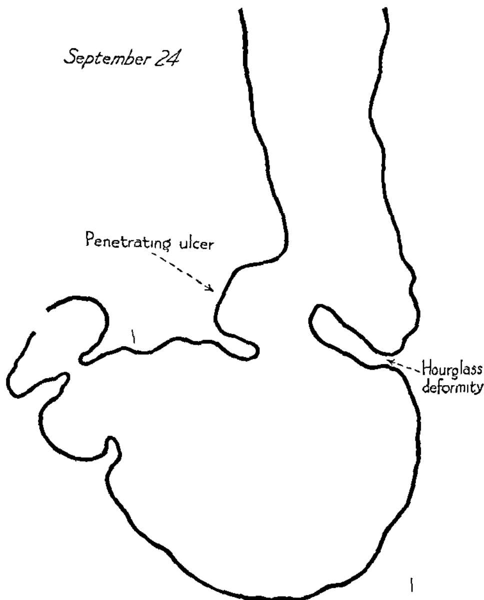


Fig 8 No 1 Mr C L age 45 Very chronic large gastric ulcer with hour glass deformity

frequently a yeasty odor (d) the finding of yeast and sarcinae in abundance in gastric contents (e) the succussion sign in the morning before breakfast

An ulcer in the wall of the pylorus or in the stomach or duodenum adjacent to the pylorus may cause obstruction by setting up persistent spasm of the pyloric

sphincter Pylorospasm is a far more important factor in the pyloric obstruction of ulcer than is generally known Furthermore the inflammatory tumefaction and edema present in varying degrees in all chronic ulcers may so encroach upon the lumen of the antrum or the duodenum as to produce appreciable degrees of stenosis As will be made clear later in discussing the treatment of ulcer it is necessary to possess an understanding of the role played by muscle spasm inflammatory swelling and edema in the mechanics of pyloric obstruction In contradistinction to the inevitably permanent obstruction of cicatricial stenosis the above mentioned causes of obstruction are relievable by medical treatment

For clinical purposes it is convenient to differentiate between low grades and high grades of obstruction the latter term applying to pyloric stenosis of such extent that the stomach retains food from one day to the next unable to empty itself during the night hours The succussion sign in the morning before breakfast with readily visible peristaltic waves moving across the epigastrium and the presence in the gastric contents of sarcinae and of food taken the day previous constitute positive diagnostic evidence of such a grade of obstruction Lesser degrees of obstruction may be diagnosed when aspiration of the stomach, at a time when it should be empty yields appreciable quantities of retained food and secretion Pyloric obstruction as a complication of ulcer profoundly influences the method of treatment Hence it is of the greatest importance that various degrees of obstruction should be recognized when present

Excessive Continued Secretion — Normally the fasting stomach contains 15 c c to 50 c c of gastric juice When appreciably larger amounts of gastric juice can be aspirated repeatedly from a fasting stomach at intervals for several hours continued secretion may be diagnosed The conditions under which such a continuous secretory functioning of the gastric glands arises and the manner in which it influences the symptom picture of ulcer have been described The diagnosis is established most readily by completely emptying the stomach at bedtime and again aspirating the stomach at midnight or thereafter when instead of the normal amount of fasting stomach secretion from 100 c c to 300 c c or more of highly acid gastric juice may be recovered Continuous aspiration throughout the night by means of a gravity aspirator yields more accurate information Not infrequently the free hydrochloric acidity will be found to range between 80 and 100 Severe nocturnal, ulcer pain is explained readily by such a finding especially as the pain invariably is relieved by removal of the powerful irritant from contact with the ulcer surface Unrelieved such intense pain promotes pylorospasm with consequent increased degree of obstruction and further retention thus prolonging the irritant effect of the high concentration of free hydrochloric acid upon the ulcer In this manner a vicious circle is set up Similar aspiration results may be obtained in the morning before breakfast In case of long continued high

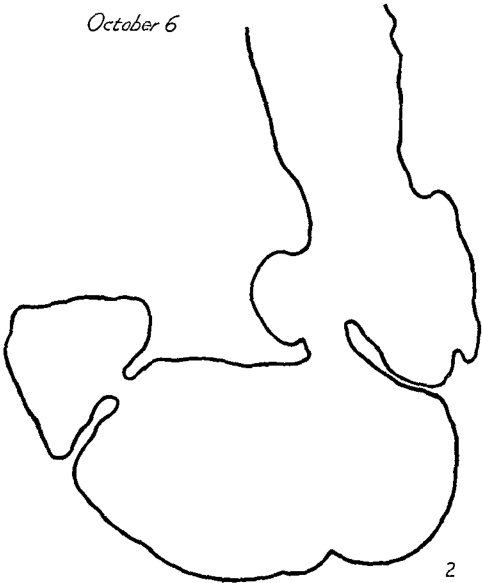


FIG 8 No 2 Same patient as shown in Fig 8 No 1 Note that rigid ulcer treatment from Sept 24 to Oct 6 carried out only from morning to evening had failed to influence the pathological change in the stomach due to untreated nocturnal continuous hypersecretion

grade, pyloric obstruction enormous quantities of highly acid gastric juice may be secreted continuously for many days even though all food and fluids by mouth be withheld The characteristic clinical picture in a case of a marked degree of

pyloric obstruction with continued hypersecretion is that of the patient who is awakened from sleep at midnight and at approximately hourly intervals throughout the night by gnawing epigastric pain each time gaining relief from a glass of milk or an alkaline power and returning to sleep only to be re-awakened as the acid curve re mounts and the pain returns

Perigastritis and Periduodenitis —Extension of inflammation to structures adjacent to the walls of the stomach and duodenum is a very common incident in peptic ulcer the pancreas being involved most frequently As a rule the inflammatory process extending beyond the base of the ulcer is confined to a relatively small area having developed so slowly that a protective wall of inflammatory exudate forms and becomes organized into adhesions which limit the extension of the process Not infrequently however such an extra gastric or extra duodenal inflammatory mass becomes large enough to produce a palpable tumor (Fig 14) The common bile duct may be compressed with resulting jaundice Such an inflammatory swelling may lead readily to the erroneous diagnosis of carcinoma Rarely an extensive perigastritis may modify appreciably the usual distress picture of peptic ulcer giving rise to pain less definitely related to food taking and less influenced by acid neutralizing agents than the characteristic pain or distress of simple ulcer Temperature rise leucocytosis exquisite local tenderness and muscular rigidity evidence an acute parigastritis but these signs mav be quite lacking in the more slowly developing type of perigastric inflammation resulting in the formation of an indurated mass which may be indistinguishable by palpation from carcinoma

Perigastric or *periduodenal abscess* may result from perforation of ulcer and localization of the ensuing peritonitis with abscess formation usually situated under the left diaphragm or between the lesser curvature of the stomach and the liver Perigastric abscess is likely to be associated with the usual signs of a confined suppurative process namely a septic type of temperature curve, marked leucocytosis and possibly a tender palpable mass in the epigastrium It is a relatively uncommon complication of peptic ulcer Perigastric or periduodenal adhesions rarely disturb the digestive function or cause abdominal distress Occasionally it is possible to diagnose an adhesive process as the basis for an upper abdominal pain or distress in an individual with either healed or active ulcer when the pain is brought on invariably by change of body posture as by turning from one side to the other Great caution should be exercised in the evaluation of x ray evidence of perigastric or periduodenal adhesions as an explanation fo otherwise obscure upper abdominal symptoms

Hour glass deformity of the stomach of various degrees results from the cicatricial contracture of the walls of the stomach so often associated with large chronic ulcers of the lesser curvature adherent to the pancreas especially when

October 23

Remnant of
ulcer crater

Fig 8 No 3 In contrast this x ray film contour shows the change produced between Oct 6 and Oct 23 in the same patient s stomach portrayed in Fig 8 No 2 by continuo s day and night acid neutralization

the ulcer involves both anterior and posterior walls of the stomach the so called "saddle back type The middle and distal thirds of the stomach are the areas commonly involved and the scar tissue narrowing of the lumen of the stomach

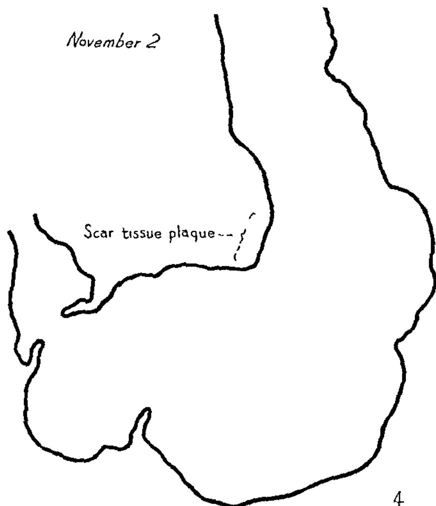


Fig 8 No 4 Note healing of ulcer and disappearance of spastic hourglass contracture in this patient whose stomach findings have been portrayed in Fig 8 Nos 1 2 and 3 from continuation of continuous day and night acid neutralization

may attain such proportions as to cause prolonged retention of food in the upper sac Peristaltic waves may be seen The condition produces no characteristic variation of the ulcer symptom picture The diagnosis is made readily by x ray examination care being taken to avoid confusing the fixed tissue hour glass deformity with transient deep incisurae of the greater curvature due to spasm (Fig 8) A marked degree of hour glass contraction especially when situated *in the*

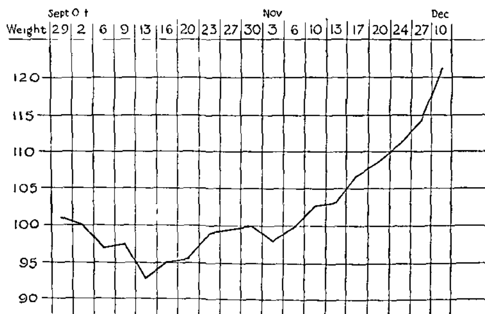


FIG 8 No 5 Weight chart of patient in whom the progress of healing of the gastric ulcer has been shown by x ray film contours in Fig 8 Nos 1 2 3 and 4

upper third of the stomach where surgical measures are hazardous, is of importance chiefly in respect to the handicaps it imposes on the medical treatment of the associated large callous ulcer

Perforation is the most serious complication in peptic ulcer By no means rarely this grave occurrence is the result of the rapidly destructive effect on the tissues of the stomach wall of an acute ulcer existent possibly for only a few days and very often quite symptomless prior to the catastrophic moment of perforation Such an acute recently formed ulcer frequently less than 1 cm in diameter, may rapidly penetrate the successive layers of the stomach wall, and if situated so that when the serosa is reached no neighboring organ is available for attachment by the plastic exudate thrown out the unprotected breech in the serosa permits gastric contents free access to the peritoneal cavity

Instantly the patient suffers severe epigastric pain and the muscle wall of the abdomen becomes fixed with a degree of board like rigidity found in no other acute abdominal condition The subsequent symptoms depend in part upon the amount of gastric content extravasated If perforation occurs at a time when the stomach contains very little material it is possible for the peritonitis to become localized and walled off by a rapidly formed plastic exudate, with gradual subsidence of symptoms and recovery According to the observations of Singer[4] it is probable that spontaneous recovery from acute perforation occurs much more

commonly than is generally believed Within a period of 18 months 40 cases of the formes frustes type of perforated peptic ulcer acute perforation with spontaneous recovery, were collected from the material of the Cook County Hospital Quoting Singer, the cases of spontaneous recovery from perforating ulcer in which the stomach and duodenum are not exposed at operation are as a rule those in which a mistaken clinical and pathological diagnosis usually of appendicitis is made

Far more often the pain becomes increasingly severe and more widespread as the peritonitis becomes general vomiting is likely to occur the facies take on a pinched drawn appearance the pulse rate increases and the extremely rigid abdominal wall becomes somewhat retracted The temperature may be normal or subnormal The leucocyte count may not be increased Air may pass through the perforation in amount sufficient to be demonstrable under the right diaphragm by x ray and in all cases in which the diagno is is in doubt the presence or absence of air between the liver and diaphragm should be determined by x ray

The prognosis is in direct proportion to the timeliness with which surgical measures are instituted If unrelieved by operation as should never happen the abdomen gradually becomes distended and tympanitic the temperature rises the pulse becomes rapid and small in volume the face pale and slightly cyanotic, beads of perspiration appear on the forehead and death occurs in from 2 to 4 days from sepsis

By far the most common site of acute perforating peptic ulcer is on the anterior wall of the stomach near the pylorus and on the anterior wall of the duodenum The sequence of events in perforation occurring in the course of chronic peptic ulcer is in no wise different from that of acute or subacute ulcer A history of previous pain or distress of ulcer type when obtainable greatly facilitates proper diagnosis of the surgical emergency however

*It should be emphasized that in certain cases the initial intense pain immedi*ately following perforation may subside and leave the patient *in a state of com*parative comfort for some hours during which a more or less general *peritonitis* is b ing established The relative comfort and deceptive excellent general status of the patient at this stage may render diagnosis difficult especially if no history of previous ulcer symptoms is obtainable

Under such circumstances the greatest assistance may be had from careful examination of the abdomen which will reveal a quite unexpected degree of muscular rigidity clearly indicating the existence of peritonitis and pointing the way to a correct diagnosis of perforating ulcer in a patient who may be insistent, at the time, upon his state of comparative well being Statistical evidence as to the incidence of perforation is extremely variable but it is probable that it occurs in from 3 per cent to 4 per cent of ulcer cases

July 13, 1945

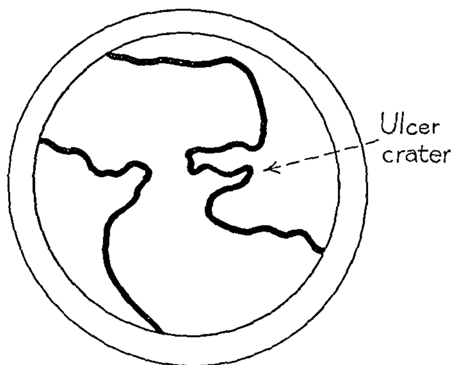


Fig 9 No 1 Mr F S age 67 Subacute penetrating ulcer of the pylorus as shown in x ray film contour of July 13 Symptoms present for 3 weeks following period of great nervous stress No previous history of dyspepsia High gastric acidity occult blood in feces marked degree of local tenderness in right epigastrium Note progressive lessening in size of defect under medical treatment with complete disappearance within 4 weeks as shown in subsequent figures

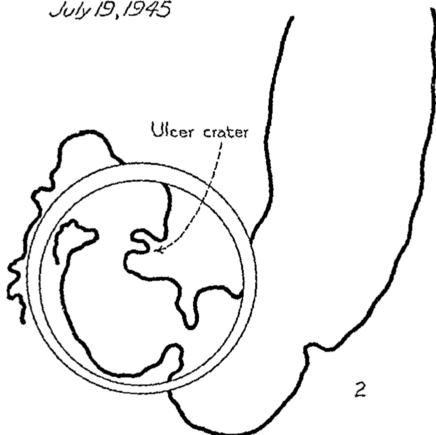


Fig 9 No X ray film contour of patient described in I gen l under Fig 9 No 1 showing condition on July 19

Differential Diagnosis

Carcinoma — In the vast proportion of cases seen clinically the diagnosis of organic disease of the stomach narrows down to consideration of two common forms of pathological lesion, namely carcinoma and peptic ulcer Ulceration is a feature common to both and one may simulate the other not only in the way of mimicry of symptoms physical signs and gastric acidity values but with respect to the x ray findings as well Thus it is necessary to consider in detail the differential diagnosis of these lesions

It is generally recognized that carcinoma of the stomach occurs as a rule in

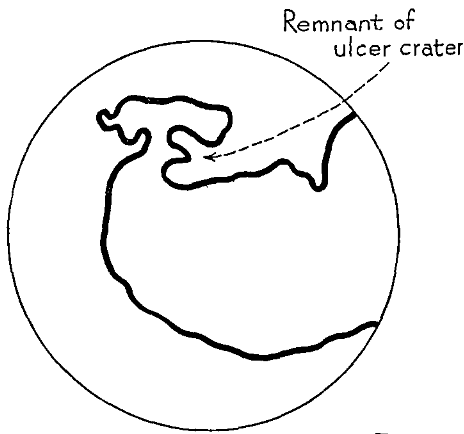


Fig 9 No 3 X ray film contour of patient described in legend under Fig 9 No 1 showing condition on Aug 1

individuals who during their lifetime have been singularly free from indigestion All too frequently, by the time medical advice is sought, the symptoms and physical signs combined with the laboratory and x ray findings are so conclusive as to cause little difficulty in diagnosis

In past years extraordinary differences of opinion have been expressed as to the frequency of cancerous degeneration in ulcer of the stomach Fortunately,

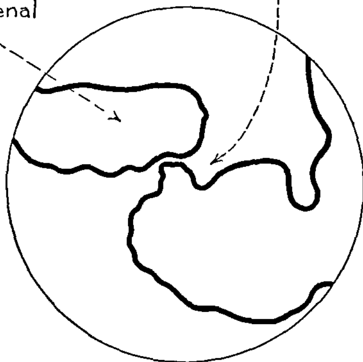


Fig 9 No 4 X ray film contour of patient described in legend under Fig 9 No 1 showing condition on Aug 10 ulcer defect has disappeared

however a clearer conception of this matter now obtains, and it is known that the great weight of evidence indicates that gastric ulcer relatively seldom undergoes cancerous change Ewing [3] reviewed the literature exhaustively and reached the conclusion that carcinoma develops from ulcer in less than 5 per cent of cases Hauser collected the statistics from seven prominent pathologists the combined figures yielding an average of 3 4 per cent of cancerous transformation in 1 774

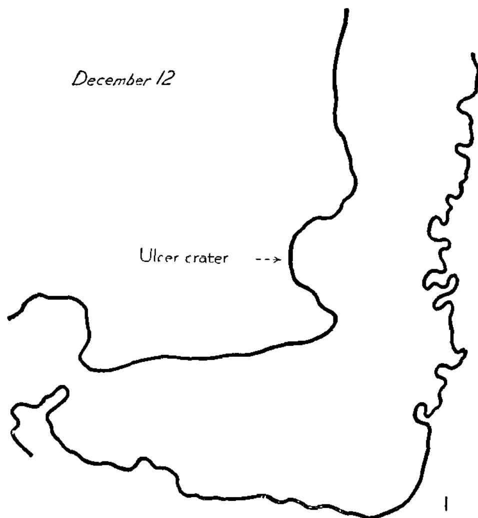


FIG 10 No 1 Mr J M age 64 Acute penetrating gastric ulcer with hemorrhage and perigastritis Status upon admission marked pallor emaciation daily temperature range 101 to 103 F epigastric rigidity hemoglobin 5 7 gm erythrocytes 1 680 000 leucocytes ,300 Patient suffering excruciating pain Later when secretory tests were possible free HCl was found to be 73 and total acidity 85 X ray film contour on Dec 12

cases of ulcer Of particular value is the evidence as to the occurrence of carcinoma after operation for gastric ulcer Luff [5] reports the results of operation for gastric ulcer in 645 cases One of the lines of inquiry followed was the incidence of gastric cancer in this large series After histories were obtained in 406 cases in 85 per cent of these cases final report was made from 4 to 9 years after gastric

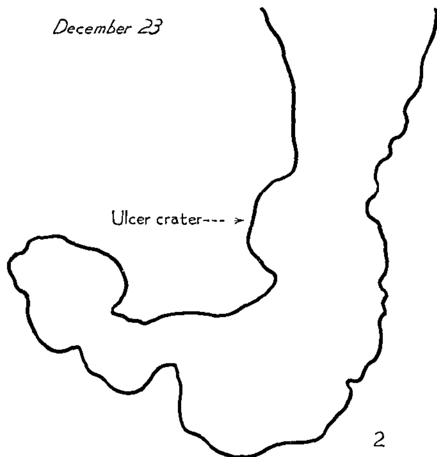


FIG 10 No 2 X ray film contour on Dec 23 showing gastric condition of patien described in Fig 10 No 1

ulcer was proven at operation According to Luff, not a single authenticated case of carcinoma developed from these ulcers There can be no doubt however that in a very small proportion of cases malignant degeneration of gastric ulcer does cccur as well as the fact that early carcinoma of the stomach may cause symptoms and yield laboratory and x ray findings similar to those of benign ulcer *A sound clinical viewpoint to adopt is to view with suspicion every ulcer of the stomach until it has been proved to be benign Fortunately such proof is not difficult to* obtain in the vast majority of cases Briefly this proof consists in (a) complete disappearance of the ulcer defect as determined by x ray examination and (b) complete and permanent disappearance of occult blood in the stools

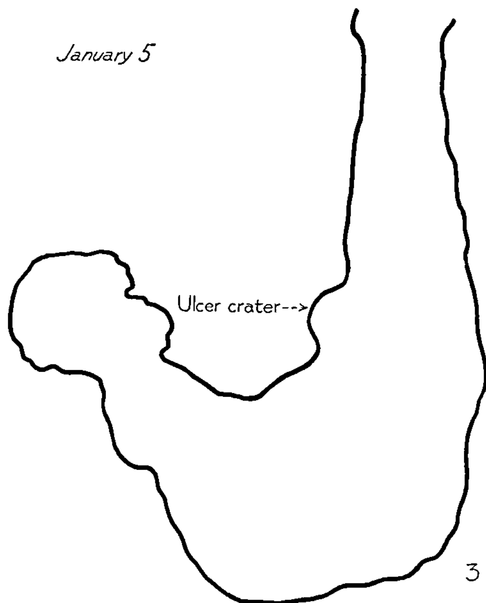


Fig 10 No 3 X ray film contour on Jan 5 showing gastric condition of patient described in Fig 10 No 1

Fortunately it is true that, in general, benign gastric ulcer heals more rapidly under accurate medical treatment than many rather refractory types of duodenal ulcer especially those based on the pancreas Furthermore it is much easier to visualize and record roentgenographically the progressive disappearance of a pene

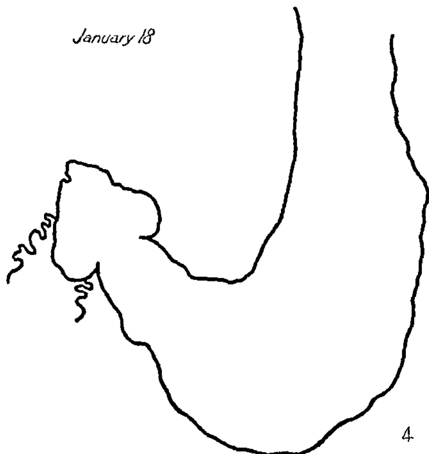


FIG 10 No 4 X ray film contour on Jan 18 of patient described in legend under Fig 10 No 1 showing that 6 weeks after treatment all x ray evidence of the lesion had disappeared and patient rapidly regained normal health This status continued for two and one half years (checked by x ray) when a small ulcer recurred in the scar tissue plaque and the stomach was resected

trating gastric ulcer than is likely to be possible in duodenal ulcer, where more or less deformity of the contour of the cap usually persists after cicatrization of the ulcer As a routine procedure every gastric ulcer under treatment should be x rayed every 10 days until the niche disappears, and if progressive lessening in the size of the crator cannot be demonstrated one of two conclusions may be drawn namely either the treatment has been inaccurate in that there has been a failure to effectively neutralize HCl or the lesion is carcinoma Benign gastric

ulcer of moderate dimensions commonly will disappear completely, as far as x ray findings are concerned, within 3 to 5 weeks of the initiation of effective treatment (Figs 9, 10 and 14) Such rapidity in the healing process cannot be expected, however unless the patient is placed at bed rest and under good management Very large and deeply penetrating gastric ulcers may not completely disappear until after a longer period of treatment (Fig 1)

Special emphasis must be laid upon complete disappearance of the x ray defect because of the fact that a definite improvement in the x ray appearance of a cancerous ulcer may occur after a period of ulcer therapy This is due to the fact that a certain amount of inflammatory reaction commonly is present in the stomach wall adjacent to the neoplasm and under the influence of bed rest, a very bland diet and in the cases of carcinomatous ulcers associated with relatively high HCl acid neutralization there may occur a sufficiently marked degree of subsidence of this inflammatory tunefaction to lessen appreciably the size of the defect as seen in x ray films However, if the lesion is carcinoma, *it will not disappear* progressively and completely as will be true of a very high percentage of benign peptic ulcers subjected to proper treatment The occasional very chronic, benign gastric ulcer in which it is impossible to secure complete healing, should be resected Such ulcers are likely to be very large and of great chronicity Under treatment healing will occur to such a degree that only a very small niche remains Failure of final healing in these cases need not be assumed to be due to malignancy but rather to the poor nutrition of the tissues due to obliteration of the blood supply by scar tissue The benign character of such lesions can be determined by the total disappearance of occult blood in the stools

Determination of the presence or absence of occult blood in the feces is of prime importance in differentiating benign and malignant ulcer The stools of the patient with benign gastric ulcer under sound treatment commonly will become free from occult blood within 10 days Persistence of occult blood for 3 or 4 weeks even when the x ray findings appear favorable must arouse a strong suspicion of malignancy and justifies resort to surgery It must be noted that a very small scirrhous carcinoma of the stomach may not ulcerate and hence may cause no occult blood in the stools This type of gastric carcinoma may be difficult to diagnose by *x ray* examination since it may cause merely some deformity of the rugae pattern and yet it may cause early metastases Fortunately such cases are rare, but they must be borne in mind as sources of error in the differential diagnosis of benign and malignant gastric lesions

The literature contains many statements to the effect that ulcer situated in the prepyloric area is more likely to be malignant than ulcer elsewhere in the stomach That this is a false assumption is shown by a review of Mayo Clinic cases, which had been diagnosed roentgenologically prepyloric ulcer by Kirkland and Mac

Carty[46] Their pathological study of a large series of cases supports the newer view that prepyloric ulcers are not more often carcinomatous than ulcers in other areas of the stomach A routine procedure on the writer s service is to instruct every gastric ulcer patient to return for x ray examination at intervals of 3 to 4 months for 1 year after discharge from the hospital

Gall bladder Dyspepsia — It is generally believed that gall bladder disease may cause symptoms and findings readily confused with those caused by peptic ulcer Diagnostic errors due to inability to differentiate between these two lesions are apt to occur only when conclusions are based upon very superficial examination Chronic gall bladder dyspepsia may occur with a time relationship to food taking similar to that of ulcer and the nocturnal pain so frequently present in individuals having gall bladder pathology may strongly suggest the possibility of ulcer with pyloric obstruction especially in cases in which the pain is recurrent many nights in succession However although there are many exceptions to this statement there is likely to be a history of typical gall stone colic at some time in the past Also the distress of the diseased gall bladder will not be relieved uniformly by food and alkalis and the time of appearance of distress after meals will lack the clock like regularity of ulcer pain Finally the results of x ray studies usually are decisive

Irritable (Spastic) Bowel — The functional disorders of the digestive tract caused by nervous stress and strain anxiety loss of sleep and chronic fatigue in the susceptible individual unfortunate enough to have inherited an unstable vegetative nervous system are well known In such an individual the effect of various stresses and strains upon the nervous system may manifest themselves in various functional disturbances of the circulatory and respiratory systems causing nervous forms of dyspnea palpitation and tachycardia, but far more commonly the digestive tract is affected most frequently in the form of hypertonus of the musculature of the stomach and colon

The epigastric distress caused by hypertonicity of the large intestine may simulate the milder types of ulcer discomfort to a degree sufficient readily to cause errors in diagnosis errors however, which usually are avoidable by careful inquiry into any coincident disturbance of bowel function and particularly into the time relationship of the distress to food taking Bowel discomfort is not so sharply localized as the ' finger point pain of ulcer and is apt to shift about from time to time, whereas the localization of pain in the ulcer sufferer remains constant The spastic bowel likely will be readily palpable especially in the sigmoid area as a rope like tender contracted tube whereas the physical sign of significance in ulcer is the single point of tenderness in the epigastrium

Functional Dyspepsia — Reference has just been made to the epigastric discomfort caused by spasticity of the bowel Certain other purely functional types

of distress require brief consideration in the differential diagnosis of peptic ulcer, the most commonly encountered being the retrosternal "heart burn" due to regurgitation of acid chyme into the esophagus, the mucous membrane of which is sensitive to hydrochloric acid Since this burning distress is diffuse, extending usually throughout the length of the esophagus, it should never be confused with the pain of ulcer, which is almost always sharply localized in the epigastrium More rarely diffuse epigastric burning pain, occurring one or two hours after eating as a persistent, chronic disorder, may be seen Many of these cases have no hydrochloric acid The mechanism of the discomfort is uncertain The gastroscopic picture of chronic gastritis may or may not be present

Treatment

Principles of Treatment

It is necessary to recognize that peptic ulcer is the local, pathological manifestation of a disease in which all of the facts relating to its etiology and pathogenesis are as yet not known The pathological changes in the stomach and duodenum are the result of a combination of causes some of which are remote from the stomach Hence while it is necessary to treat and, if possible, heal the ulcer, it is equally important to direct medical therapy to the correction of the underlying causes of ulcer disease insofar as these causes are now known

Foci of infection, having a possible etiological relationship to an ulcer under treatment most often will be discovered in the course of examination of the teeth, the tonsils and the accessory nasal sinuses The removal of infected tonsils and of devitalized teeth showing any evidence of periapical infection is important When the teeth have been removed the alveolar processes should be x rayed for evidence of chronic osteitis such as may persist for years about the remnants of a tooth It is advisable to insist upon the treatment of pyorrhea alveolaris as well Chronic sinusitis should be eliminated when possible, by such surgical and medical measures as may be deemed appropriate

The Acid Factor — The direct digestive agent the peptic action of the gastric juice, immediately concerned in the formation of the ulcer defect and thereafter an integral factor in the chronicity of ulcer obviously must be dealt with in any process of treatment

Ulcer of the stomach and duodenum occurs only in the presence of free hydrochloric acid Pepsin is inactive in an alkaline or neutral medium The belief is universal that healing of ulcer is promoted by such measures as free the granulating surface of the ulcer from the digestive action of the gastric juice The problem of treatment of the lesion then resolves itself in large part into a question

of methods of annulling the action of pepsin by instituting such measures of treatment as will decrease in some degree the secretion of hydrochloric acid and will neutralize as completely as possible whatever quantity of hydrochloric acid is secreted

The types of ulcer treatment in vogue in the earlier years especially those of Leube and Lenhartz, were based on the idea of minimizing the corrosive action of the gastric secretion by the use of bland foods and small amounts of alkalis Sippy, recognized that the chief hindrance to healing is the destructive proteolytic action of gastric juice on the exposed surface of an ulcer and that even a minimum amount of free hydrochloric acid is sufficient to make pepsin an active solvent for albuminous substances laid down as the basic objective of treatment the maintenance of an accurate *neutralization of all free hydrochloric acid* during the time that food and its accompanying gastric secretion are present in the stomach thus protecting newly formed granulation tissue from digestion and permitting the natural reparative processes to bring about cicatrization of the lesion The validity of this basic principle in the treatment of peptic ulcer is recognized universally Innumerable observations have been recorded to establish the facts relating to the effectiveness of the application of this principle to the treatment of ulcer

Treatment of Non-Obstructive Type

Rest — The clinical concept of peptic ulcer as a simple round or oval defect in the wall of the stomach or duodenum of greater or lesser depth all too frequently fails to include an understanding of the great extent of the inflammatory swelling of the tissues surrounding the ulcer crater In cases of ulcers of considerable chronicity the inflammatory mass thus formed may attain or exceed the size of an egg and frequently is firmly adherent to the pancreas or liver The treatment of such an inflammatory process requires immobilization as surely as does an inflamed knee joint and the patient who is permitted to remain ambulatory and physically active during the initial period of ulcer treatment is far less likely to become well than one who is placed at rest The ulcer patient should be confined to bed for from 2 to 3 weeks and this period should be prolonged in the treatment of large deeply penetrating ulcers and in many hemorrhagic ulcers Thereafter violent exercise and sports such as tennis hand ball and horseback riding should be avoided for at least 2 months

Diet — The indications require the arrangement of a diet having a relatively large content of albumen capable of neutralizing hydrochloric acid as well as sufficient fats to depress appreciably the secretion of hydrochloric acid The diet should be palatable and bland free from substances likely to irritate mechanically or chemically the surface of the ulcer and with a caloric value adequate

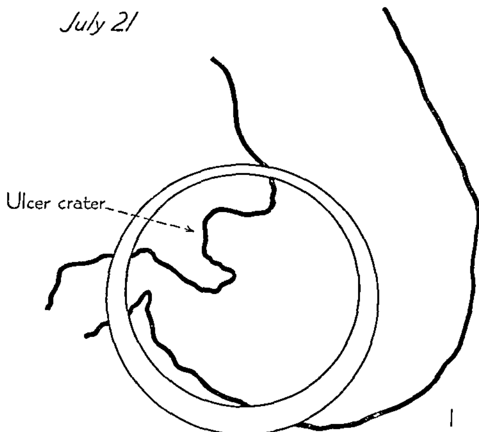


FIG 11 No 1 Mr B T age 59 X ray film contour on July 21 showing large gastric ulcer of 4 months duration with deep crater Agonizing pain especially during the period from midnight to three o clock A M Free HCl 98 clinical units Note rapid healing (Fig 10 No 1) under continuous acid neutralization using milk drip during the night hours Recurrence 3 months later (Fig 11 No 3) Wide gastric resection was done immediately Ulcer base found adherent to pancreas Uneventful recovery Postoperative fractional meal with histamine yielded free HCl 20

to the nutritive requirements of the patient It should contain the necessary vitamins

Cruveilhier (1791-1874) distinguished pioneer in the field of gastric pathology advocated an exclusive milk diet in the treatment of peptic ulcer and milk has continued to form the basis of the dietary management to the present day When supplemented by orange juice it contains all the elements essential to a suitable diet Moreover its peculiar adaptability to the treatment of ulcer lies in the fact that it contains sufficient protein to enable a given volume of milk to neutralize approximately an equal volume of 0 3 per cent hydrochloric acid, as

shown by Freezer Gibson and Matthews[47] (1928), so that milk may be used not only as the principal item of nutrition but as the chief acid neutralizing agent as well The effectiveness of a milk diet in the treatment of ulcer is enhanced greatly by the addition of cream, not only on account of its caloric value but because of the well known influence of fats in depressing the secretion of hydrochloric acid as originally observed by Pavlov who showed that in the stomach of a dog 600 c c of cream produced only 18 9 c c of gastric juice secretion in comparison with 37 7 c c of secretion resulting from a similar volume of milk

Ninety c c 3 ounces of a mixture of equal parts of milk and cream are given each hour from eight in the morning until seven in the evening With the gradual addition of various bland foods from time to time this schedule of milk and cream feedings is continued for whatever variable period of time usually several months may be deemed necessary to insure healing of the individual ulcer This amount of full milk and 22 per cent cream totalling 1 080 c c (36 ounces), contains approximately 1 500 calories Midway between the milk and cream feedings small amounts of alkalis are given in doses just sufficient to effect complete neutralization of free hydrochloric acid in the chyme during the second half of the hour After the last feeding in the evening an alkali is administered each half hour for 4 doses to insure maintenance of a state of hydrochloric acid neutralization until the stomach is approximately empty In this simple manner it is possible to protect the granulating surface of the ulcer from the corrosive peptic action of the gastric secretion from morning until evening thus removing the single greatest known hindrance to healing

While it is entirely practical to limit the diet strictly to milk and cream for many weeks it is neither desirable nor necessary to do so Many ulcer patients are seriously undernourished and require diets of higher caloric content and there are many bland foods which may be appropriately added to increase the nutritive value of the diet and obviate the monotony of an hourly milk and cream feeding schedule Provided the basic principle as laid down by Sippy is adhered to, namely the maintenance of *complete hydrochloric acid neutralization* from breakfast until bedtime the selection of the various items of bland foods to be included in the diet may well be left to the initiative of the attending physician It should be strongly emphasized at this point that the successful treatment of ulcer is a highly individual matter Rigid adherence in all cases to formal schemes of treatment is not likely to be productive of the best results Poached or soft boiled eggs thoroughly-cooked cereals including cream of wheat rice and oatmeal creamed soups other than tomato, vegetables in puree form a portion of baked or mashed potato with butter or cream soft toast custards fruit jellies blanc mange and sponge cake may be included in the diet as well as cottage cheese gelatines and ice cream As it is unwise to stimulate gastric peristalsis by single

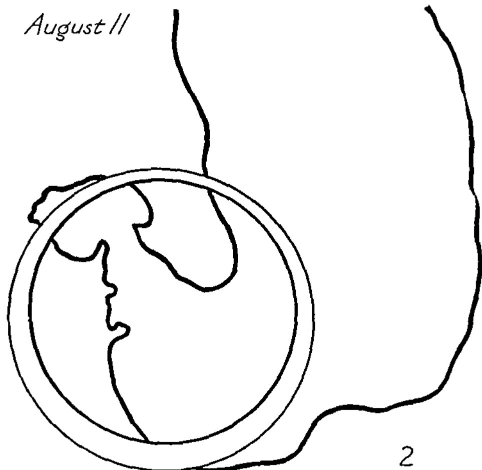


FIG 11 No 2 X ray film contour on Aug 11 of patient d cribed in legend of Fig 11 No 1 showing healing

large feedings it is advisable to give these foods in the form of frequent small feedings throughout the day Thus a serving of some one or other of the bland items named may be added every second day from the beginning of the treatment, until at the expiration of 2 weeks the patient will be taking some type of food every 2 or 3 hours in addition to the hourly feeding of milk and cream If desired these extra feedings may replace the milk and cream at any given hour During the early weeks of treatment the total quantity of any one feeding should ordinarily not exceed 180 c c 6 ounces Obviously the amount of food given in addition to the hourly milk and cream will be governed largely by the nutritional requirements of the patient Orange juice in 3 ounce amounts should be ordered 3 times daily from the initiation of treatment

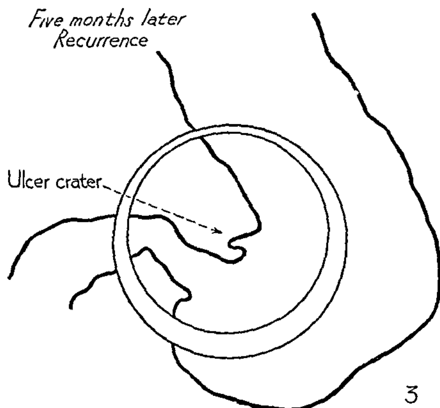


FIG 11 No 3 X ray film contour 5 months after Fig 11 No 2 howing recurrence of ulcer This ulcer then healed after ga tric resection

After 3 to 4 weeks of adherence to this very bland diet somewhat more latitude may be allowed the patient especially as ordinarily he will be resuming at this time his usual occupation and taking 3 meals daily Thus any thoroughly cooked cereal not containing bran may be taken untoasted bread not too freshly baked may be used and tender cooked vegetables such as asparagus tips beets carrots peas and squash which by thorough mastication can be reduced to a fine state of subdivision need not be pureed A wide variety of cooked fruits and deserts including simple puddings may be added It has been shown that raw fruits and vegetables in a state of coarse subdivision are retained in the stomach appreciably longer than when finely subdivided by cooking and sieving Secretion of gastric juice continues so long as food remains in the stomach hence salads pickles pineapple cabbage raw apple nuts and other items which are

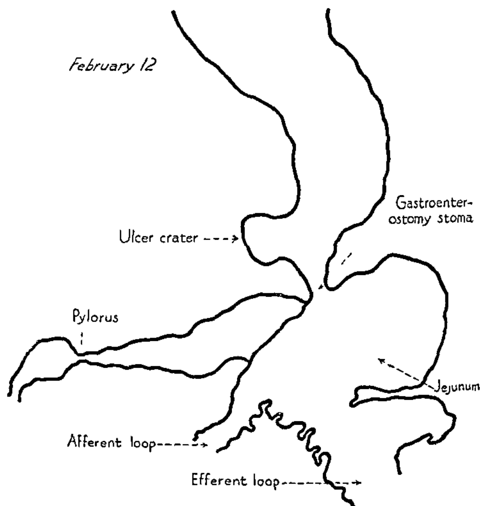


FIG 12 No 1 Mr T D age 66 X ray film contour of large gastric ulcer occurring 5 years after gastroenterostomy performed for obstructive duodenal ulcer This gastric ulcer formed in a stomach with a perfectly functioning stoma and very rapid emptying time No previous gastric ulcer Fig 12 No 2 shows stomach after ulcer healed No recurrence 10 years later

likely to be ingested in a mechanically coarse state, should be avoided, as well as the chemical irritants present in mustard chili, vinegar and spices The skins and seeds of fruits should be eliminated

Gastric juice secretion is stimulated by the extractives of meat (Pavlov), hence meat and meat soups should be taken only in very moderate quantities during the period of ulcer treatment Limited portions of breakfast bacon chicken and fresh

fish and an occasional lamb chop or tender portion of beef may be allowed Strong alcoholic drinks should be avoided

Alkalis — Through further development of the hormonal inhibition of gastric secretion along the lines of the work of Ivy[48] with enterogastrone it may some day be possible to maintain an acid free state in the stomach of the ulcer bearing individual for a period of time sufficient to permit the ulcer to heal without other treatment but at present it is possible to achieve or approximate this objective medically only by the use of one or more of the many acid binding substances available Milk protein is an excellent, acid neutralizing agent especially when used in the manner of a continuous milk drip However it is not practically feasible to keep ulcer patients on continuous milk drip type of management exclusively for the entire period of time required for the healing of chronic peptic ulcer useful as the procedure is in the initial stages of treatment of certain types of ulcer notably those with pyloric obstruction and continued nocturnal secretion In very few cases of peptic ulcer, as seen clinically can the free hydrochloric acidity be entirely neutralized throughout the day and evening by hourly feedings of milk and cream

Repeated bedside tests have shown that in the average case of ulcer with acid values somewhat higher than normal the neutralizing action of 90 c c (3 ounces) of a mixture of milk and cream keeps the chyme free from uncombined hydrochloric acid for approximately one half hour To maintain complete neutralization during the second half hour (until time for the next milk and cream feeding) accurate treatment demands the use of some type of alkali to be administered hourly midway between the milk and cream feedings The alkalis in most general use for this purpose at the present time are the tribasic phosphates of calcium and magnesium calcium carbonate bicarbonate of soda and magnesium oxide Although a powerful anti acid having nearly four times the neutralizing power of bicarbonate of soda relatively little magnesium oxide can be used because of its strong aperient effect

Sodium bicarbonate has several distinct disadvantages It expends its neutralizing effect too rapidly liberates a large volume of carbonic acid gas which distends the stomach, and it has a decided tendency to cause marked disturbance of the acid base ratio as shown by Gatewood[49] and his co workers Furthermore, if it is given in excess of the amount required to effect neutralization an undesirable secretory phase may result since it has been shown that when the pH of the gastric content rises appreciably above pH 7 0 a counter hyper secretion of hydrochloric acid may follow The use of sodium bicarbonate in routine ulcer treatment was abandoned by the writer many years ago as a result of observations on the frequency with which it caused disturbance of the acid base ratio in the blood serum

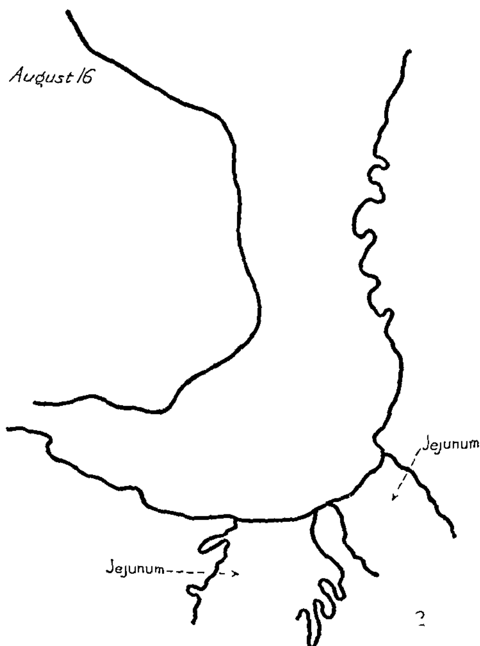


FIG 12 No 2 From same patient as depicted in Fig 12 No 1 showing healing after treatment

For data on the acid neutralizing power of various substances we are indebted to Freezer, Gibson and Matthews[a] (Table II) The figures were obtained by titrating a constant weight of 'alkali' (0 2 gm) with 0 3 per cent HCl

TABLE II

	Vol (cc) of Acid Neutralized	
	In 5 min	In 10 min
Bismuth oxycarbonate	0 5	0 5
Calcium carbonate	5.8	20 25
Milk (10 cc)	11.05	11 00
Tribasic magnesium phosphate	15 05	19.95
Potassium citrate	17 20	17 20
Tribasic calcium phosphate	10 05	21 25
Sodium citrate	18 10	18 10
Sodium bicarbonate	29 70	29 70
Magnesium carbonate (basic)	43 15	48 65
Magnesium peroxide	47 50	56 40
Magnesium oxide	94 10	110.45

("Alkali" used in each case = 0 2 gm)

The majority of ulcer patients possess an excellent tolerance for calcium carbonate due to the fact that any excess of the salt above the quantity required for neutralization of free acid in the stomach is excreted unchanged in the feces as shown by Loevenhart and Crandall[51] The calcium chloride formed in the stomach from its union with HCl is reconverted in the intestine into calcium carbonate Calcium carbonate may produce toxic symptoms in susceptible individuals by causing a relative alkalemia but with much less frequency than bicarbonate of soda It has approximately two thirds the neutralizing power of bicarbonate of soda In the average ulcer patient especially when the hydrochloric secretion is coincidently depressed by giving belladonna 1 3 gm (gr 20) of calcium carbonate taken midway between the milk and cream feedings will neutralize effectively the free hydrochloric secretion The precise dosage may be determined readily by aspirating the stomach one half hour after the administration of the alkali namely at the time when the next milk and cream feeding is due, preferably late in the afternoon If free HCl is present upon repeated tests using dimethyl amido azobenzol as an indicator, 0 3 gm (gr 5) of calcium carbonate should be added to the quantity in use and the tests continued Rarely will less than 1 gm (gr 15) or more than 1 6 gm (gr 25) be required Since calcium carbonate frequently exerts a somewhat constipating effect, it is well to give magnesium oxide 0 6 gm (gr 10) in substitution for the calcium carbonate as many times during the day and evening as may be necessary to insure adequate bowel movements

The tribasic phosphates of calcium and magnesium were proposed as alkalis especially suitable to the treatment of ulcer by Kantor (1923)[5] and by Shattuck, Rhodenburg and Booher in 1924 It is believed that they are excreted entirely by the bowel and thus exert no general systemic alkaline effect The writer has made extensive use of these tribasic phosphates and rarely has observed any toxic effects from their continued administration in doses adequate to control effectively the gastric acidity

Since the calcium salt is slightly constipating, and the magnesium salt is mildly laxative it is necessary to combine the two in such proportions as are proper for the individual patient The average hourly dosage is, approximately, tribasic calcium phosphate 1 3 gm (gr 20) tribasic magnesium phosphate 1 gm (gr 15) In every case under treatment the actual neutralizing effect of the alkali should be checked by aspiration and titration until the exact amount required by the given case has been determined precisely

Aluminum hydroxide in colloidal form causes no disturbance of the acid base balance and has a somewhat limited usefulness in ulcer therapy In the process of binding HCl aluminum chloride is formed This is quite astringent, frequently causing nausea and abdominal distress when aluminum hydroxide, in the large amounts sufficient to actually neutralize the gastric acidity, is given Breuhaus and Eyerly [4] determined by electrometric measurements of the pH of the gastric juice made in situ that 7 to 10 minutes are required for 10 c c of the usual liquid preparation to bring 30 c c of 0 17 N HCl to pH 3 5 According to these writers 10 c c of aluminum hydroxide amphojel has only slightly more than one half of the neutralizing power of 1 gm (gr 15) of calcium carbonate However, despite its relatively low effectiveness as an acid binder it has a certain usefulness in ulcer patients who have an idiosyncrasy to alkalis

Toxic symptoms may be caused by the administration of certain alkalis in common use in the treatment of ulcer As will be pointed out later in the discussion of the treatment of the obstructive group of ulcers alkalosis is observed chiefly during the course of management of duodenal ulcer with obstruction, high hydrochloric acid values and a continued secretion requiring neutralization during the night hours, especially in cases in which large quantities of gastric juice are removed from the body either by the tube or by vomiting It must be recognized however that alkalosis symptoms are not limited solely to this group of cases Patients advanced in years do not tolerate alkalis as well as the young, and any marked degree of impairment of the renal function is likely to be a serious handicap in the use of alkalis in the treatment of ulcer Rarely, young or middle aged ulcer patients without pyloric obstruction or other complication and with functionally normal kidneys may show a peculiar and as yet unexplained intolerance to the use of moderate doses of certain alkalis especially bicarbonate of soda and

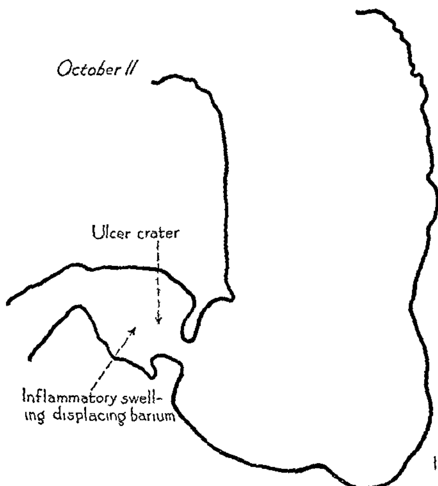


FIG 13 No 1 Mr W M age 17 X ray film contour showing crater ulcer in posterior w ll of duodenum surrounded by ufficient inflammatory swelling to completely displace barium in area adjacent to the crater X ray film was taken on Oct 11 without pres ure over duo lenal cap by either hand or pressure cone

calcium carbonate an intolerance which may or may not be reflected in dis turbance of the acid ba e ratio in the blood serum

Initial symptoms of a lack of tolerance to alkalis as used in the routine treat ment of ulcer are headache thirst loss of all desire for food and mental depres ion e pecially during the later hours of the day If the cau e of the symptoms is not recognized and the alkali in use discontinued more serious symptoms are

likely to ensue The headache becomes more continuous and intense, polyuria develops with tendency to rapid dehydration of the patient, the skin becomes harsh and dry and the tongue parched, there is great thirst, the patient becomes restless and irritable and nausea and vomiting set in to intensify the dehydration process Albumen appears in the urine the plasma carbon dioxide combining power may range from 80 to 110 per cent, and the blood chlorides may fall below 300 mgm If the alkali is not withdrawn at this stage, muscular twitching, delirium coma and death may follow rapidly In such a case seen by the writer in consultation many years ago a few hours before death occurred, the clinical picture was that of uremia with clonic convulsions Enormous doses of bicarbonate of soda had been used recklessly in the treatment of a duodenal ulcer

Toxic symptoms such as have been described, need never be permitted to develop beyond the very earliest harmless manifestations Upon the first appearance of symptoms of alkalemia all alkalis should be withdrawn for a period of 3 or 4 days during which time 60 c c (2 ounces) of milk and cream are given at half hourly intervals thus lowering the gastric acidity to a marked degree and supplying the necessary food and fluids The toxic symptoms rapidly disappear The type of ulcer treatment to be used subsequently will depend upon the individual case Many ulcers will heal on a continuation of milk and cream taken at half hourly or even hourly intervals between meals, with alkaline powders taken only in the evening or it may be possible for the patient to tolerate approximately one half the amount of alkali which caused symptoms In such a case routine treatment may be resumed alternating an alkaline powder with 24 c c (6 3) of aluminum hydroxide Marked degrees of intolerance to alkalis in individuals having very chronic deep seated ulcer is a somewhat infrequent indication for surgery

Illustrative of the extreme degree of disturbance of the chemistry resulting from loss of chlorides by vomiting and the simultaneous taking of bicarbonate of soda is the case of E K male aged 59 admitted to the writer s service at Presbyterian Hospital in February 194- He had had recurrent ulcer symptoms for many years During the preceding 6 weeks he had been awakened repeatedly at night by pain relieved by sodium bicarbonate and by vomiting very large volumes of gastric content which in recent days had greatly exceeded the amount ingested He was weak and emaciated and in a state of extreme dehydration Stomach aspiration upon admission yielded 2 500 c c of fairly clear fluid with free HCl 45 total acidity 80 Blood serum CO vol per cent 140 4 chlorides 330, total non protein nitrogen 61 Almost complete anuria Twenty four hours later after emergency measures the CO vol per cent had dropped to 89 4, chlorides rose to 400, total non protein nitrogen to 100 urea nitrogen to 80 and uric acid to 12 3 Total serum protein was 5 62, albumin 3 22 and globulin 2 40 Broncho



Fig 13 No 2 X ray film contour of same patient as depicted in Fig 13 No 1 taken 6 weeks later Evidence of ulcer has disappeared

pneumonia and hyperpyrexia developed and he died 42 hours after admission Autopsy revealed a large penetrating callus ulcer just proximal to the pyloric ring causing stenosis Without medical advice he had been taking great quantities of sodium bicarbonate to relieve ulcer pain

Ulcer patients having any considerable degree of impairment of kidney function are likely to have a low tolerance for even the tribasic phosphates In such cases surgical treatment is advisable if the lesion is so situated as to be amenable to operation In connection with the consideration of the toxic symptoms which may result from the use of alkalis it should be emphasized again that one of the

likely to ensue The headache becomes more continuous and intense, polyuria develops with tendency to rapid dehydration of the patient, the skin becomes harsh and dry and the tongue parched, there is great thirst, the patient becomes restless and irritable and nausea and vomiting set in to intensify the dehydration process Albumen appears in the urine the plasma carbon dioxide combining power may range from 80 to 110 per cent and the blood chlorides may fall below 300 mgm If the alkali is not withdrawn at this stage, muscular twitching, delirium, coma and death may follow rapidly In such a case seen by the writer in consultation many years ago a few hours before death occurred the clinical picture was that of uremia with clonic convulsions Enormous doses of bicarbonate of soda had been used recklessly in the treatment of a duodenal ulcer

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painful and demands relief as a result of its tendency to cause pyloric obstruction thus rendering itself subject to greatly prolonged hours of corrosion by a highly acid chyme

Justification for considering the treatment of ulcer associated with pyloric obstruction under a separate heading is found in the fact that failure in the recognition and proper treatment of pyloric obstruction and the commonly associated continued gastric juice secretion is undoubtedly a principal cause for many of the failures in medical treatment The management is the same in principle as that described for the non obstructive type and is carried out in precisely the *same way during the day and evening If a considerable degree of pyloric obstruction is present* the stomach will contain at bed time from 500 c c to 1 000 c c of food and secretion and it is essential that this be aspirated by means of the stomach tube The chief stimulus to an excessive nocturnal secretion thereby is removed Routinely the stomach should be emptied in this way one half hour after the last powder namely at 9 30 in the evening and during the first few days of treatment a second aspiration should be made at midnight to determine the presence or absence of an abnormal continuous night secretion This information may be obtained more accurately by the use of a Rehfuss or Levine tube introduced after the stomach is emptied at bedtime and left in place until 1 00 A M or throughout the night if necessary Aspirations of the stomach through such an indwelling tube either intermittently every half hour or continuously by the use of a gravity (Wangensteen) aspirator will determine whether or not a continuous hypersecretion exists as a complicating factor Volumes of 500 c c to 1 500 c c or more may be found with free HCl as high as 105 clinical units If no more than the upper limit of normal in amount of fasting stomach secretion (50 c c) is found upon one or more midnight aspirations it may be assumed that *no special means of treatment other than the bedtime aspiration are required during the night hours* However if at midnight the tube yields from 100 c c to 200 c c or more of clear highly acid gastric juice it is obvious that progress in healing of the ulcer will be jeopardized until this abnormal night secretion has been controlled Fortunately removal by bedtime aspiration of the normal stimulus to such a secretion by keeping the stomach free from food during the night hours ordinarily results in the subsidence of the night secretion to normal limits *within a week or 10 days of the beginning of the ulcer treatment*

Continuous nocturnal hypersecretion is treated simply and effectively by using throughout the night hours a continuous milk drip in the manner first suggested by Winkelstein[5] After aspirating and lavaging the stomach at 9 30 P M in the usual manner a Levine tube well lubricated with mineral oil is introduced into the stomach through the nasal passage and attached to an irrigation flask containing 1 500 c c of milk the flow of which is regulated by a pinch cock to

most important facts to be determined during the early weeks of treatment is the precise amount of alkali required to effect neutralization Observance of this technical point will obviate the danger of alkalosis except in the rarest instances

Theoretically one might expect the alkalis used in the treatment of ulcer to cause renal stone Kretschmer and Brown[5] found however that the difference of 1 8 per cent in the incidence of stone formation between individuals, who were given alkalis in the treatment of ulcer and in those who were not, is so insignificant as to make it improbable that alkalis used in ulcer treatment play a role in stone formation

Atropine and *belladonna* having a depressant action on gastric secretion, are useful adjuncts to the acid binders in ulcer treatment Atkinson and Ivy [6] ascertained the effect of atropine on gastric secretion in dogs with Pavlov pouches, using both food and histamine as secretory stimulants and found a reduction in the volume of gastric juice secreted over a 2 hour period of about 50 per cent, as well as a slight rise in titratable acidity The decrease in volume represented a considerable diminution in the total number of milligrams of HCl secreted over a 2 hour period To be effective atropine or the more commonly used tincture of belladonna must be given in doses approaching the limit of tolerance as indicated by dryness of the mouth and blurring of vision and this will be found to vary over a considerable range in different individuals It is not possible to obtain an acid free stomach from its use alone

Treatment of Pyloric Obstruction Type

Pyloric obstruction of appreciable degree is a common result of the pathological changes which occur in the course of the life history of duodenal ulcer or of gastric ulcer seated near the pylorus Abnormally long retention of food and acid secretion in the stomach result Inevitably there are longer periods of time each day during which the surface of the ulcer is subjected to peptic corrosion The longer the duration of acid corrosion the greater the amount of pain likewise the greater the tendency to hemorrhage to perforation and to retardation of healing As the pain increases pylorospasm becomes more pronounced the obstructive factor thus is increased, and in this manner a vicious circle is set up which profoundly influences the physiology of the stomach as well as the symptom picture and clinical course of ulcer situated at the outlet of the stomach

Duodenal ulcer is recognized and treated by both internists and surgeons with far greater frequency than gastric ulcer although statistical reports from the pathologists show that ulcer is more common in the stomach than in the duodenum The natural inference to be drawn is that gastric ulcer unassociated with food stagnation very often is relatively symptomless while duodenal ulcer becomes

Since the protein of the milk ordinarily is not adequate in acid binding power to completely neutralize the very high acid values of the average nocturnal hyper secretion it is necessary to add from 0 8 to 1 gm (gr 12 to 15) of sodium bicarbonate to each ounce of milk in the irrigating flask The precise amount of sodium bicarbonate to be added can be determined readily by aspirating through the Levine tube once during the night and testing for free HCl

It should be borne in mind that nocturnal hypersecretion may occur also in association with large chronic gastric ulcer distant from the pylorus and when discovered requires the same treatment as the abnormal secretion caused by pyloric obstruction Rarely will it be necessary to continue the use of the milk drip for longer than 10 nights due to progressive subsidence in the volume of the hypersecretion under ulcer treatment

Three factors enter into the clinical and pathological picture of pyloric obstruction due to active duodenal or prepyloric gastric ulcer namely pylorospasm inflammatory swelling and scar tissue narrowing of the pylorus or duodenum As a rule all three of these obstructive factors are present in variable degrees Of basic importance in the treatment of obstructive ulcer is the fact that inflammatory swelling and pylorospasm rapidly subside under good medical management leaving only whatever degree of cicatricial narrowing may be present in a given case as the sole factor capable of hindering normal emptying of the stomach Fortunately *the above two relievable causes of pyloric obstruction are the dominant causes of obstruction* in the majority of cases which means that only a fraction of the cases which are obstructive when seen by the physician require surgery for permanent scar tissue stenosis Stating the point in a different manner *many cases of peptic ulcer with high grade pyloric obstruction can be converted by* medical treatment into simple uncomplicated ulcer with the stomach emptying in normal time as effectively as can be done by gastroenterostomy and within a few weeks time The frequency with which such results are obtained by medical measures may be illustrated by the statement of Lahey[63] that less than one third of the ulcer patients entering his surgical clinic with pyloric obstruction have required operation It must be emphasized however that such results are not obtained unless the stomach is emptied by tube at bedtime for as long as may be necessary and any existing continued secretion controlled in the manner described

Disappearance of the obstructive factors is signalized by progressive lessening of the amounts obtained by bedtime aspiration of the stomach and by fluoroscopic observation which will reveal lessening or disappearance of spasm and widening of the lumen (Fig 4) It is advisable to postpone a final conclusion as to any permanent degree of stenosis until after 6 weeks of medical care If there is then sufficient stenosis to interfere appreciably with normal gastric motor function surgery is advised especially in the young and middle aged If however the patient

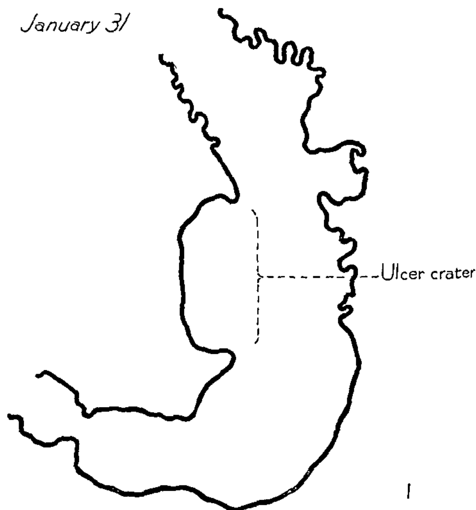


Fig 14 No 1 Mrs A P age 55 X ray film contour on Jan 11 Enormous gastric ulcer with perigastritis of such extent as to form a palpable mass filling the entire epigastrium from midline to costal border History of epigastric pain for 3 months with nausea and vomiting and loss of 38 pounds of weight in this period Upon admission to hospital the temperature was 100 F leucocytes 11 600 erythrocytes 4 200 000 and patient was in a state of marked starvation acidosis Occult blood in feces Some days later an Ewald yielded free HCl 35 total acidity 49 Figs 14 No 2 and No 3 show the very rapid rate of healing under medical management and Fig 14 No 4 the final fixed scar tissue placqu

about 40 drops per minute The patient is given a simple sedative to counteract the slight discomfort of the tube and usually sleeps throughout the night the tube being removed in the morning when routine ulcer management is resumed

permanent scar tissue pyloric obstruction who for any reason may be a poor surgical risk usually can obtain not only complete relief but by the simple expedient of a bedtime a piration each night gain most of the benefit to be had from gastroenterostomy namely an empty stomach from bedtime to breakfa t time

Treatment of Hemorrhage

A review of the literature of the past decade dealing with gross hemorrhage from peptic ulcer reveals disturbing variations in the mortality figures reported by various experienced physicians Furthermore as a result of the apparent failure of current methods of medical treatment to save more lives endangered by massive hemorrhage the surgeons have taken a hand urging immediate operation in severe life threatening hemorrhage especially in the age group over fifty years and their experience is also available

Portis and Jaffe reported that in a series of 9 171 consecutive necropsies per formed at Cook County Ho pital 1929–1936 hemorrhage as a cause of death was observed in 0 43 per cent of all necropsies and in 18 3 per cent in which peptic ulcer was seen as the essential lesion Chiesman[6] reported the heavy mortality rate of 25 per cent in patients admitted for ulcer hemorrhage to St Thomas Hos pital London during a 6 year period 1925–1931 A striking fact as well as a probably explanation for this very high death rate is that only 15 of the 191 cases reported were given blood transfusions Blackford and Cole[61] had a mortality rate of 15 per cent in 57 cases of massive hemorrhage and of 8 per cent in their entire series of 113 cases of active hemorrhage of all degrees

One of the most comprehensive recent reports is that of Rafsky and Wein garten[6] who summarized the experience with 408 patients with bleeding peptic ulcer treated in various divisions of two hospitals from 1927 to 1941 Of these more than half 270 patients were under 50 years of age and of these 13 died a mortality of 4 8 per cent In the group over 50 years of age 138 patients 23 died a mortality of 16 6 per cent In 18 of the 408 cases or 4 4 per cent hemorrhage was the sole cause of death In 18 other cases 4 4 per cent complicated diseases contributed to the mortality The mortality for the entire series of hemorrhage cases was 8 8 per cent Various types of treatment were used including that of Meulengracht In the group of 39 cases placed on this form of treatment the mortality rate was 10 3 per cent

Meulengracht [3] gives all hemorrhage cases a full pureed diet alkalis bela donna and large doses of iron from the day of admis ion to the hospital The diet given is as follows

Six A M Tea white bread and butter

Nine A M Oatmeal milk white bread and butter

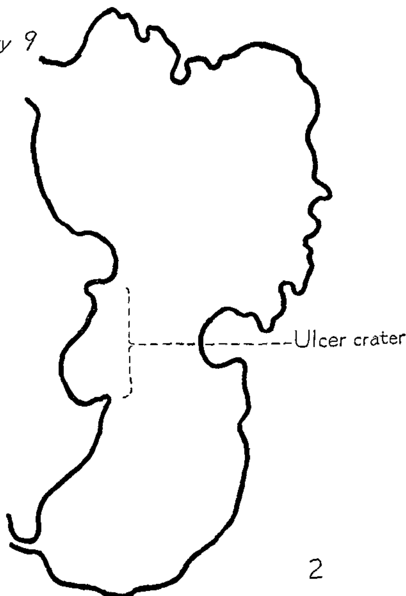


FIG 14 No 2 X ray film contour on Feb 9 showing progress of healing of ulcer in patient described in legend of Fig 14 No 1

prefers to continue medical management he may safely do so just so long as he may elect to continue emptying the stomach with the tube at bedtime Finally, with the ulcer healed he abandons all measures except thorough mastication of food and the bedtime aspiration In this way an ulcer bearing individual with

proximately 9 per cent of all duodenal ulcer patients coming to the Massachusetts General Hospital have massive, acute bleeding and that 13 per cent of these die from acute anemia if treated conservatively A summary of our data reveals that nearly all patients under the age of 45 will spontaneously recover from acute bleeding, while approximately 30 per cent of those above this age will succumb In his opinion success is likely if operation is carried out within 72 hours Eight out of 9 patients so operated upon recovered However in 6 cases that had been bleeding for more than 7 days operation resulted in the death of all but 1 patient Rankin and Coleman [6] also strongly emphasize the necessity of early operation if emergency surgery is to be undertaken for critical hemorrhage Operation must be performed within the first 48 hours and preferably the first 24 hours' They state that a surgical mortality rate of 5 to 15 per cent may be expected

The decision to resort to emergency surgery in a critical case of hemorrhage will inevitably, be a difficult one There may be uncertainty regarding the site and the character of the bleeding lesion The patient already is suffering from some degree of shock and the question of the surgical risk involved becomes paramount Furthermore if the emergency measures presently to be described are immediately carried out the death rate from massive hemorrhage from peptic ulcer can be lowered to a point even in the age group over 50 years which cannot be hoped for from surgery Bohrer [7] reports a postoperative mortality of 17 8 per cent in 160 cases of bleeding ulcers of all types which were operated upon during the period of active bleeding No cases from the writer s service have been referred to surgery for emergency operation for acute massive hemorrhage during the past 15 years

Before proceeding to a discussion of the details of the treatment of gross hemorrhage from peptic ulcer a summary of the experience of the writer and his associates * at the Presbyterian Hospital is presented Since 1930 201 patients with gross hemorrhage in the form of hematemesis melena or both have been admitted on the service and of this number only 4 died from hemorrhage a mortality rate of 2 per cent In determining this overall mortality rate it should be noted that only 1 of these 4 deaths resulted from blood loss unassociated with other complicating factors Thus 1 death occurred in a man of 50 an alcoholic who was known to have hepatic cirrhosis Upon admission because of profuse hematemesis it was assumed that the hemorrhage was from esophageal varices Within 24 hours he became comatose developed bilateral Babinski sign and other evidences of toxic encephalopathy dying without regaining consciousness At no time did the erythrocyte count drop below 2 800 000 Necropsy however showed in addition to cirrhosis a duodenal ulcer with an eroded artery He had had no subjective symptoms of ulcer The second complicated hemorrhage death was that of

* Dr James B Eyerly and our assistants whose courtesy is acknowledged

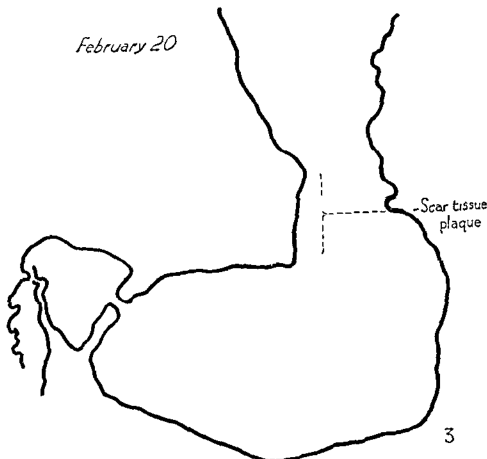


FIG 14 No 3 X ray film contour on Feb 20 showing progress of healing of ulcer in patient described in legend of Fig 14 No 1

One P M Dinner including a wide variety of dishes
Three P M Cocoa
Six P M White bread and butter meat cheese and tea

The patient is allowed to eat as much as he desires It should be noted that Sippy far antedated Meulengracht in applying the principle of using food, in the ideal form of milk early in ulcer hemorrhage treatment Meulengracht reports a mortality rate of 2 per cent in a large series of cases of gross hemorrhage

A comparison of the Meulengracht and Sippy types of treatment was made by Emery[64], who treated a group of 36 hemorrhage cases according to Meulengracht and another group of 50 cases in general more severe by the Sippy regime and found the mortality results approximately the same

The surgical point of view has been expressed by Allen[65], who states that ap

Thus it will be seen that, if the 2 cases of hemorrhage in which there were grave pathological processes other than ulcer are excluded namely the cirrhosis and the perigastric abscess cases the mortality rate from hemorrhage in this series of medically treated cases would be 1 per cent a figure lower than any heretofore published

For purposes of statistical study this group of cases of gross hemorrhage from ulcer, the diagnosis in each case being confirmed by x ray operation or necropsy has been divided into four grades of severity of hemorrhage using as an index the erythrocyte count at its lowest This is by no means a wholly satisfactory basis for estimating the gravity of a massive hemorrhage as illustrated by a case (S K aged 57), placed in grade II, because his red cell count at no time was recorded as being below 3 000 000 although for a week he passed enormous quantities of dark red blood by bowel and was considered to be in a desperate condition He received 17 blood transfusions during a period of 11 days thus maintaining a relatively good erythrocyte count Similarly and because of the liberal use of transfusions, many of the cases classified according to the blood count as only moderately severe hemorrhages were in fact far more critical However, the erythrocyte count supplies the most precise evidence available (Table III)

Particular attention is directed to the figures in the above table respecting the age groups There is an almost universal belief that severe hemorrhage in individuals over 50 is associated with a high death rate Thus in this age group Rafsky and Weinstein[6] had a mortality of 16 6 per cent Allen[65] is of the opinion that 30 per cent will die if treated conservatively, and Blackford and Williams [8] state that prompt surgical intervention for critical bleeding from ulcer in older patients seems to offer the only hope of reducing the present mortality rate which is above 30 per cent Reference to Table III will show that in this series of cases of gross hemorrhage 94 of the patients were over 50 years of age If the 2 fatal cases already described as deaths due largely or chiefly to complicating factors namely (1) hepatic cirrhosis and (2) perforated gastric ulcer with abscess be excluded from the hemorrhage mortality figures as reasonably they may be it will be seen that there were no deaths solely from exsanguination in this series of patients over 50 years of age

An individual actively bleeding from peptic ulcer requires immediate hospitalization The death rate from critical hemorrhage is likely to be directly proportionate to the speed and skill with which emergency measures are carried out by an alert and well trained medical service A rough estimate of the blood loss and of the seriousness of the hemorrhage may be made at once from the history and the condition of the patient A hemoglobin reading and erythrocyte count are helpful but will fail to yield accurate figures regarding the actual degree of anemia when made the first day or two after a sudden, severe hemorrhage Only

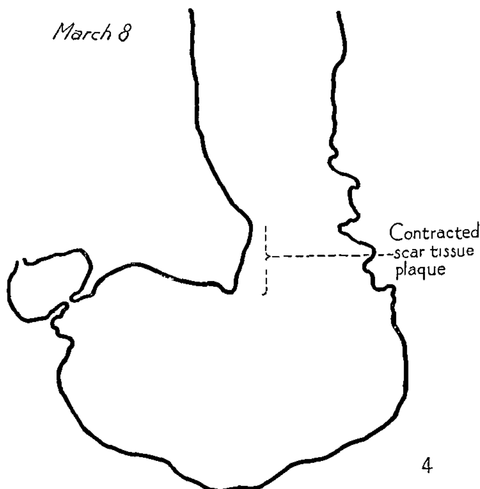


FIG 14 No 4 X ray film contour on March 8 showing progress of healing of ulcer in patient described in legend of Fig 14 No 1

an emaciated woman 66 years of age who had upon admission a large perigastric abscess resulting from acute perforation of a gastric ulcer 3 weeks prior Her admission status was temperature 102° F leukocytes 19,000, patient semi moribund too poor a surgical risk to operate upon She died immediately following a gastric hemorrhage of moderate amount The remaining case was that of a man aged 25 who had had a gastroenterostomy for duodenal ulcer later bleeding from jejunal ulcer Subtotal gastric resection was followed by another jejunal ulcer, and he was resected again A large ulcer then formed in the very small remaining fundic portion of the stomach eroding the anterior surface of the pancreas and the splenic artery, causing death from hemorrhage and exhaustion

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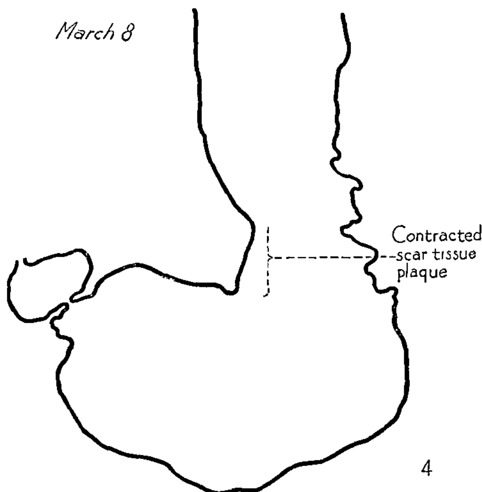


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aspirating bulbs of good suction power The tip of the stomach tube should be introduced to a point just below the cardiac orifice (the esophageal opening is approximately 16 inches from the incisor teeth), and through the tube bulb ful quantities of ice cold water are successively and rapidly introduced into the stomach and immediately withdrawn As the stomach may be filled with clotted blood which has the same stimulating effect upon the gastric secretion as any other albuminous substance the lavage should be continued until the water re turns relatively clear following which as much of the lavage water as possible is withdrawn, the entire procedure ordinarily requiring from 5 to 10 minutes Im mediately thereafter 15 c c (½ ounce) of 1 to 1 000 adrenalin solution may be given by mouth as an additional local hemostatic agent A slow absorption of adrenalin occurs sufficient to cause a very moderate rise in the blood pressure which of course usually is extremely low in cases of critical hemorrhage The use of adrenalin in this manner has been criticized because of this effect upon the blood pressure but in combination with ice water gastric lavage it has been used as an emergency measure in very many desperate cases of hemorrhage with no observable ill effect

Hemorrhage ceases as a result of clot formation, but a blood clot is digested by *gastric juice as readily as egg albumen hence the necessity for as early and* complete neutralization of HCl as possible Since it is desirable to minimize the volume of the gastric content as well as peristaltic activity the amount of milk given at hourly intervals is limited to 2 ounces for the first 2 or 3 days small amounts of orange juice and water also being permitted Alkaline powders are ordered as in routine ulcer management The patient is kept in bed and if unduly restless and apprehensive, is given morphine sulfate 8 to 10 mgm (gr ⅛ to ⅙) and atropine sulfate 0 3 mgm (gr 1/200) every 4 to 6 hours

It is not without significance that so many ulcer hemorrhages occur during the early morning following long night hours of acid corrosion due to pyloric obstruc tion and continued nocturnal secretion In the management of gross hemorrhage it is imperative that any existing continued night hypersecretion be dealt with effectively The clue to the presence of this complicating factor usually is found in the history of pain in recent weeks which has awakened the patient from sleep and every bleeding case should be questioned carefully regarding this If evi dence suggestive of pyloric obstruction or continued nocturnal hypersecretion is *found* the daytime treatment of the bleeding case must be supplemented by a continuous milk drip throughout the night in the manner already described and this must not be abandoned until it is certain that all bleeding has ceased and the patient is in condition for the carrying out of the usual diagnostic procedures It is probable that more lives are lost from hemorrhage as a result of failure to neu tralize such a nocturnal hypersection than from any other single cause Cessation

TABLE III

MORTALITY IN GROSS HEMORRHAGE FROM PEPTIC ULCER UNDER MEDICAL TREATMENT

	Number of cases	Average erythrocytes	Patients under 50 years	Patients over 50 years	Deaths	Age at death
Grade I Erythrocyte count 4 000 000 and over	21	4 235 000	11	10	0	
Grade II Erythrocyte count 3,000 000 to 3 990 000	70	3,330,000	40	30	0	
Grade III Erythrocyte count 2 225 000 to 2 990,000	69	2 694 000	34	35	1	50
Grade IV Erythrocyte count less than 2 225 000	41	1 798 000	22	19	3	28, 40, 66
Total	201	3 014 000	107	94	4	

after the normal fluid volume of the blood has been regained will the blood count accurately reflect the amount of blood loss

If the hemorrhage is of a critical type or even moderately so, a blood transfusion should be given as soon as a suitable donor can be obtained, and at the same time arrangements must be made for the availability of other donors The early and liberal use of blood transfusions has proven to be a major factor in lowering the death rate from hemorrhage When the volume of blood suddenly lost has been great and there is unavoidable delay in securing a compatible blood donor, normal salt solution should be given intravenously to aid in restoring the circulating fluid volume

The gravity of the emergency in a given case obviously depends upon the degree of exsanguination and the rate at which the loss of blood is continuing if at all The latter point may be difficult to determine in cases in which there is melena only the best indications being the pulse rate, the color of the skin and mucous membranes and the frequency and volume of tarry or dark red evacuations If the blood loss has been great and if there is reason to believe that bleeding is continuing the most effective way to stop the hemorrhage is to lavage the stomach with ice cold water employing for the purpose an Ewald tube and

emptying time of the stomach surgery should be advised for the relief of the obstruction

The type of operation will depend in part upon the age and condition of the patient and the ease with which the stomach can be mobilized for high resection in part upon the individual predilections of the physician and the surgeon The first gastroenterostomy was performed by Wolfler in 1881 and by the end of the first decade of this century the operation had gained such popularity as to be considered almost a panacea for benign gastric disorders Thus Mikulicz [?] writing regarding the question of the wisdom of excision of gastric ulcer said the almost certain cure of these patients by gastroenterostomy alone makes other operations unnecessary And in 1910 Moynihan [?] stated in my opinion the treatment of a chronic duodenal ulcer should always be surgical and in the very great majority of cases the operation of gastroenterostomy is the most applicable and in its results the most satisfactory

In 1924 Balfour[71] voiced the opinion that there is no operation more useful than gastroenterostomy in cases of duodenal ulcer except in carefully selected cases The operation in suitable cases can be depended on to give excellent and permanent results in more than 90 per cent of cases It is now recognized however that the incidence of jejunal ulcer following gastroenterostomy is very high about 16 per cent and since this lesion is a very troublesome one usually requiring resection of the stomach the trend in recent years has been definitely away from gastroenterostomy in favor of wide gastric resection

The surgical objective in subtotal resection is to obtain if possible an acid free stomach or at least one which if not wholly acid free will have permanently a greatly reduced acidity This highly desirable objective is however difficult to achieve Thus Friedell Shaar and Walters conclude that 75 per cent of patients undergoing gastric resection will have relative achlorhydria and that of these about 25 per cent will have practically absolute achlorhydria Kiefer[73] found that 68 per cent of 141 resected cases showed no free HCl following a 45 minute Ewald meal but that 16 out of 23 of these negatives showed free HCl when histamine was given If following resection the stomach is acid free with histamine the patient may be assured of freedom from ulcer recurrence but with even a low free acidity there is a certain degree of risk of jejunal ulcer formation Of the 68 cases from the writer s service which were resected 52 were tested postoperatively chiefly by fractional methods and of these exactly one half showed free HCl the titration values averaging free HCl 22 In this group of 68 gastric resections there were 10 cases in which jejunal ulcer occurred subsequently Excluding 2 cases in which only partial resection had been done there were 8 cases, 12 5 per cent of jejunal ulcer following wide resection

Removal of the major portion of the gastric mucosa may have certain deleteri

of gross hemorrhage is evidenced by the appearance of a light colored stool However it is essential to continue to examine the movements daily, until they are found to be wholly free from occult blood, before it can be assumed that bleeding has ceased completely Whatever degree of anemia may be present will require appropriate treatment a 50 per cent solution of ferric ammonium citrate, 2 cc (30 minims) t i d being useful

Indications for Surgical Treatment

Perforation into the peritoneal cavity requires immediately laparotomy, the only exception to this rule being the "formes frustes" type of perforation in which a rapidly formed plastic exudate walls off the peritonitis and confines it to a relatively small area In such a case the decision for or against laparotomy will depend upon the findings in each individual case If there is no air between the liver and the diaphragm and if the area of upper abdominal wall rigidity is not extensive and the general condition of the patient is good it may be reasonable to place the patient under constant observation for a few hours at absolute rest and with nothing taken by mouth If after a few hours the physical findings indicate that the peritonitis still is well localized and all other indices such as temperature, leucocyte count and subjective symptoms are favorable, this conservative treatment may be continued In such case subsidence of the signs of local peritonitis are likely to be observed within 48 hours When it is deemed safe to allow foods to be taken routine ulcer management is instituted

Cicatricial pyloric obstruction is the most common indication for surgery, as shown by the fact that of the 1 500 cases of ulcer admitted to the service of the writer and his associates at the Presbyterian Hospital since 1930 161 patients 1 06 per cent were referred to surgery, and of this number 117, 72 per cent, were so referred because of scar tissue obstruction from chronic duodenal or prepyloric peptic ulcer

In describing the clinical picture and course of ulcer causing pyloric obstruction of varying degrees emphasis was placed upon the fact that in a major proportion of these cases certain *relieable obstructing factors* namely spasm and inflammatory swelling are the chief causes of the obstruction present when the patient is first seen and since they disappear under proper medical treatment, no conclusion as to the existence of *permanent* cicatricial stenosis requiring surgery can be drawn until after a period of medical management of some weeks Since considerable time is required for the subsidence of a large inflammatory mass such as is so often present it is well to postpone a final decision until a fluoroscopic examination is made after approximately 6 weeks of medical care If at that time a marked degree of stenosis is seen, and clinical tests show a definite delay in the

edema about the suture lines at the stoma In many cases nightly aspiration is necessary for many weeks after gastroenterostomy, since the inflammatory tumefaction of the tissues about the stoma may subside very slowly Failure to observe this precaution will increase the danger of jejunal ulcer (2) The patient should be placed on strict, acid neutralizing ulcer management for a few weeks for the purpose of more gradually conditioning the jejunal mucosa to contact with high hydrochloric acidity

Refractory Gastric and Duodenal Ulcers—Duodenal ulcers of great chronicity adherent to pancreas and thus incapable of infolding and deprived of a fair blood supply by dense scar tissue, are like large old callous ulcers of the leg notoriously difficult to heal and when proven to be refractory to medical measures require surgery Similarly there is a type of chronic gastric ulcer in which resection is necessary These ulcers usually large and of long duration fall into two groups with respect to the surgical indications In one the ulcer defect progressively decreases in size under medical treatment to the point where only a very small niche surrounded by an extensive scar tissue plaque is seen fluoroscopically Complete cicatrization of this remaining small ulcer-defect may be difficult to obtain due to its poor blood supply, and resection is advisable In the other an ulcer of the type just described has healed under medical treatment but months later recurs in the center of the scar tissue plaque due to the low vitality of the tissue (Fig 11) *When such a recurrence is recognized* the lesion should be resected immediately Of the 161 patients referred for surgery by the writer s service since 1930, only 13 were so referred because of recalcitrant gastric or duodenal ulcer or recurrence of gastric ulcer

Recurrence of Hemorrhagic Type of Duodenal Ulcer—Certain duodenal ulcers are characterized by a tendency to bleed massively at intervals of months or years many of them with little or no warning in the way of preceding subjective symptoms Thirteen cases in the writer's series were resected solely because of such recurrent hemorrhage Very many of the pyloric obstruction cases, already referred to which were sent to surgery had of course gross hemorrhage as a complicating factor Reference must again be made to the fact that all of the serious hemorrhage cases in the writer s series were treated solely by medical measures during the emergency period

Jejunal ulcer often is amenable to medical treatment if seen early but if the history indicates that the lesion has been existent for some months a gastric resection is indicated

ous effects on the subsequent health of the patient, the most frequently observed being the inability to maintain a good state of nutrition A smaller group of resected cases will have a persisting anemia which however, rarely is of serious degree Final judgment regarding the effect on the body economy of removal of so large a part of the stomach must await accurate data on a large number of resected cases thoroughly examined 10 years after operation

Gastroenterostomy certainly offers the ulcer patient requiring surgery somewhat less prospect for permanent relief than does wide gastric resection Thus of the 98 cases from the writer s service on whom gastroenterostomy was done because of obstruction, 19 cases returned with the symptoms and x ray findings of jejunal ulcer and 12 additional patients had recurrence of symptoms diagnosed as due to re activation of duodenal ulcer An excellent result was obtained in about three quarters of the cases since many who had recurrent ulcer, recovered and remained well after further medical care

The recently expressed conservative viewpoint of Heuer and Holman[74] regarding radical resection was based on careful preoperative and postoperative determination of HCl secretion in a series of 75 gastroenterostomies and 88 gastric resections of varying degrees The study was made for the purpose of comparing the range of postoperative acid values with the clinical results obtained from the operations Although they found no significant changes in acid secretion following gastroenterostomy 75 per cent of the patients had had a satisfactory result over a follow up period of 6 to 10 years In the minimal resection group, in which less than one half of the stomach was resected 74 3 per cent of the patients had postoperatively normal or higher than normal hydrochloric acidity, yet 90 per cent of these patients had had satisfactory results With wider resection, one half to two thirds of the stomach only 19 6 per cent had normal or high acidity after operation yet the end results in this group were no more favorable than in the minimal resection group Heuer and Holman suggested that the beneficial effect from both gastroenterostomy and gastric resection may be due to dilution and neutralization of gastric juice They state that if their findings are confirmed 'it would appear of doubtful value to pursue the idea of insuring achlorhydria and therefore better results by larger and larger resections It may be better to accept the limitations of resection as a treatment of ulcer and adopt an operation of lesser magnitude which insures fairly satisfactory results with a reasonable mortality and permits further surgery if recurrence takes place "

The greater the amount of pyloric stenosis the greater is the likelihood of a good result following gastroenterostomy Two postoperative measures should be invariably carried out (1) bedtime aspiration of the stomach on or about the tenth day to ascertain if the stoma is functioning properly A very marked degree of gastric retention will be found frequently due to inflammatory swelling and

Excellent reviews of this literature with bibliographies may be found in publications by Hartzell[80] in 1929 and by Alvarez[81] in 1948

In the latter half of the last century many experimental observations were made on the importance of the role played by the vagus nerves in the mechanism of gastric secretion, and in 1910 Pavlov[8] published his classic studies showing that following section of both vagus nerves in dogs there is abolition of the normal gastric secretory response to sham feeding thus proving that the psychic phase of gastric secretion is dependent upon secretory fibres carried by the vagi

During the two decades following the publication of Pavlov s work sizable series of abdominal vagotomies for a variety of gastric disorders were reported by French German and Italian surgeons Thus in 1914 Exner and Schwarzmann[82] reported having performed the operation in 20 cases of gastric crisis of tabes with beneficial results in 50 per cent of the patients and in 1922 Latarjet[83] published important observations on the physiological effects of gastric denervation in dogs as well as the results of vagotomy in 4 patients Anticipating later work of more precise character he noted the individual variations in the anatomical distribution of the vagi and commented on the intimate intermixture of the vagi and the sympathetics in their final distribution He observed that vagus stimulation in dogs produced a contraction ring in the fundus and that section of the nerves decreased the tone of the fundus causing dilatation and impairment of the motor function to such a degree that the emptying time in dogs was prolonged from 2 hours to as long as 7 hours Also the secretion of HCl seemed to be decreased but his observations on gastric secretion were incomplete

Latarjet performed vagotomy in cases of peptic ulcer tabes and a category of gastropathies without gross lesions with no operative mortality The 5 ulcer cases in his series were all gastroenterostomized at the time of vagotomy, and all had complete relief from pain gained weight and considered themselves cured However since all of this small group of ulcer cases had gastroenterostomy Latarjet cautiously reserved opinion as to the part played by vagotomy in the therapeutic result He attributed the good result of vagus section to (1) giving a measure of rest to the stomach (2) the interruption of painful reflexes originating in the stomach (3) probable decrease in gastric acidity It is interesting to note that in the discussion of Latarjet s paper the chief point raised was that of the long time effect of gastric neurectomy a question which still remains to be answered

Preparatory to all gastric surgery a study of the patient's blood chemistry should be made especially with reference to the total protein, albumin globulin and chloride content, as well as the prothrombin time, and deficiencies corrected Preoperative blood transfusions should be given for any marked degree of anemia, and an adequate supply of blood assured for postoperative use, if needed Postoperatively the same measures relating to the life and habits of the ulcer-bearing individual as are mentioned under Prevention of Recurrences, should be enforced

Finally, it is possible that with the passage of time, the surgical approach to the solution of the problem of ulcer treatment may be from a different angle This is suggested by the experimental work of Dragstedt and Owens who proceeding on the basis of the possibility that constant excessive activity of the gastric secretory fibers may be a factor in ulcer formation and continuation, sectioned both vagus nerves just above the diaphragm in 2 patients with chronic duodenal ulcer and continued nocturnal hypersecretion of very marked degree with the result that the volume of nocturnal secretion was reduced to a quarter of its preoperative figures and the acidity was greatly lowered also the patients gaining subjective relief This work now has had considerable clinical application and results have been such that the entire procedure now deserves thorough discussion as will be found in the next section Treatment of Gastric Duodenal and Gastrojejunal Ulcer by Secretion of the Vagus Nerve

Andrus and his associates[6] by implanting a pedicle graft of jejunum into the wall of the stomach produced a striking effect on gastric secretion consisting in a reduction of the fasting free acidity and a marked diminution or actual reversal of the normal response of the gastric glands to histamine They report that the operation has been applied to patients with marginal and duodenal ulcers with excellent immediate clinical results

Treatment of Gastric Duodenal and Gastrojejunal Ulcer by Resection of the Vagus Nerves

History —The historical data relating to vagotomy is of great interest Since Brodie[9] reported to the Royal Society in 1814 his observations on vagotomy in dogs a voluminous literature regarding the physiological and therapeutic effects of gastric neurectomy has accumulated

on these dogs and revealed that the gastric secretory function had returned to normal, the fractional analysis readings of free HCl and total acidity being approximately as high as those obtained by Hartzell before vagotomy

Clinical observations following vagus resection in the human show conformity with the findings of Hartzell and Vanzant in the dog Total section of the vagi in ulcer patients results in a marked reduction in gastric acidity frequently to a degree where no free HCl is present However the follow up of vagotomized patients by Moore and his associates[90] has shown that secretory changes as noted by multiple quantitative determinations of the overnight gastric secretion tend to return toward the normal range over a period of 6 to 12 months although some reduction in acidity and an increased pH value may persist The response to insulin induced hypoglycaemia, however has remained abolished in all our cases except one These investigators also state that gastric motility as recorded by the kymograph is likely to return to normal within one year following vagus section

The Insulin Test—In 1929 Okada and associates[91] showed that the hypoglycemia caused by insulin in large doses is associated with a marked gastric hypersecretion and a year or two later reported that this stimulation effect upon gastric secretion could be abolished by vagotomy Since in the application of the principle of gastric neurectomy to the treatment of peptic ulcer the necessity for *total* section of the vagus nerve supply to the stomach became increasingly stressed attention was directed by Jemerin Hollander and Weinstein[92] and later by Hollander[93] to the use of the insulin test as the best means of determining whether or not all vagus fibres had been severed in a given case Fifteen units of insulin are injected intravenously and fractional gastric analysis done after induction of a hypoglycemia of 50 mgm or less If no distinct rise in the free HCl curve occurs the insulin test is recorded as negative, presumptive evidence that all vagus fibres have been cut

Several investigators have reported puzzling experiences with the test which have raised some doubt as to its specificity but there can be no doubt that total section of the vagi results in a vast proportion of cases in absence of appreciable gastric secretory response to hypoglycemia The test is of great usefulness in the evaluation of the clinical results obtained by vagotomy and should be done routinely in every case

Vagotomy does not abolish the gastric secretory response to histamine

Dragstedt and Owens[8] in 1943 published their initial report on supra diaphragmatic resection of the vagus nerves in the treatment of peptic ulcer and to Dragstedt and his associates is due the credit for the revival of an obsolescent surgical procedure and for the present wide spread interest in what may well prove to be an effective means for dealing with ulcers which have proven refractory to medical treatment

Experimental Data —Preliminary to discussion of the physiological changes resulting from vagotomy in the human and to an evaluation of the therapeutic usefulness of the operation based on a review of the recent literature certain salient facts derived from experimental sources should be noted Beaver and Mann[86] reported in 1931 that vagotomy does not always prevent the development of ulcer in Mann Williamson dogs in which jejunal ulcer regularly forms in at least 95 per cent of the animals This was confirmed by Saltzstein and his associates[87], who performed supra-diaphragmatic vagotomy on a larger series of Mann-Williamson dogs, the neurectomy being done an average of 11 days after the Mann Williamson operation Twelve dogs survived the Mann-Williamson operation 19 days or longer and the vagotomy 12 days or longer Jejunal ulcer developed in 6 of the 8 vagotomized animals that lived more than one month after the Mann-Williamson operation Furthermore, an inflammatory reaction of varying severity was found in the upper part of the jejunum in 7 of the 12 dogs In 2 cases the jejunitis was diffuse and severe for 18 inches and 14 inches respectively The authors state that if such jejunitis should be found to exist in patients after vagotomy it might explain the diarrhoea which at times follows this surgical procedure'

Experimental work on the effect of vagotomy on gastric secretion was done in 1929 by Hartzell[88], who trained 6 dogs to aspiration of the stomach by tube until fractional analyses of the gastric contents carried out over a period of several weeks showed the animals to be well trained as evidenced by the approximately constant acid values obtained The vagus nerves then were cut intrathoracically Thereafter gastric analyses were made once or twice weekly for 1 to 5 months All of these dogs showed a marked and constant reduction in both free hydrochloric acid and total acidity The total emptying time was slightly prolonged However the fact that the effect of resection of the vagus nerves on the digestive phase of gastric secretion may be only a temporary effect was demonstrated by Vanzant[89] who made fractional gastric analyses on 3 of the dogs used by Hartzell in the research just described Vanzant's observations were made 2½ years after vagotomy had been performed

of pain clinical experiences having shown that it is immediately relieved by acid neutralizing substances the most obvious explanation is that of reduction in gastric acidity That some other factor may well play a role in the pain relieving mechanism is suggested however by the fact that freedom from pain occurs just as uniformly in cases in which there has been only a very moderate reduction in free hydrochloric acidity as in the cases in which vagotomy resulted in achlorhydria Moreover Smith and associates[97] report that the acid test was negative in 11 patients after transthoracic vagotomy whereas prior to vagotomy introduction of 0 5 per cent HCl into the stomach had produced typical ulcer pain in each case

Ruffin and White[8] cite physiological evidence which casts doubt upon interruption of sensory pathways as an explanation for the phenomenon and raise the question as to whether the pain relieving effect of vagotomy may not be due to the great diminution in peristaltic activity which is an invariable result of total gastric neurectomy Whatever the mechanism may be it is well established that following the operation patients are free from ulcer pain and with the exception of a group of cases in which unpleasant side effects appear enjoy a sense of well being and tend to gain weight

Impairment of Motor Function — The profound effect of vagotomy on the motor function of the stomach and bowel constitutes the most troublesome complication resulting from the operation For a varying period of time there is great diminution of peristaltic activity in the stomach frequently associated with marked loss of tonus, resulting in a greater or lesser degree of gastric stasis This necessitates decompression by tube or by Wangensteen suction for 4 or 5 days after operation and in certain cases for a very much longer period In the post operative management of these cases urecholine in doses of 2½ to 5 mgm subcutaneously will be found useful as a stimulant to gastric peristalsis In time in the majority of cases the intrinsic motor mechanism in the stomach wall becomes adjusted to the loss of vagal stimulation and tonus and peristaltic activity tend to return to normal the time required varying greatly, however

Some degree of epigastric discomfort of fullness and pressure type occurs in a large proportion of vagotomized patients but this also is usually transient in character A much smaller number of patients will have persistent symptoms such as epigastric distension eructations vomiting and nausea symptoms sufficiently troublesome to affect the viewpoint of the patient as to the value of the operation In the follow up

A fact not without interest is that gastric ulcer can be produced in rabbits by vagotomy Beazell and Ivy[91], investigating the role of roughage in the genesis of ulcer, performed bilateral subdiaphragmatic vagotomy on 30 rabbits Twenty-nine animals survived the operation and were given a rough diet Of these, 12 developed ulcer on the lesser curvature of the stomach Of the 15 rabbits surviving more than 50 days 66 6 per cent developed typical chronic, lesser curvature ulcers In another series of vagotomized rabbits a soft diet decreased the incidence of ulcer by half

Anatomical Considerations —With a view of determining whether the transthoracic approach possesses an advantage over abdominal section in operation for resection of the vagi Bradley and associates[9] studied the anatomy of the gastric nerves finding that in 92 of 100 cases the union into two main trunks of the fibres originating in the esophageal plexus occurred at varying levels above the esophageal hiatus In the remaining 8 cases the nerves did not follow a uniform course or pattern In some cases there was a failure of numerous fibres coursing down the esophagus from the esophageal plexus to form into trunks, thus passing on through the hiatus into the stomach in this multiple and discrete fashion The conclusion was reached that in somewhat less than 10 per cent of cases there might be difficulty in sectioning all of the vagus nerve fibres Chamberlin and Winship[28] made a similar study of 50 esophagi removed at autopsy from which they conclude that there is a group of cases of complex pattern in which there is sufficient variation from the usual distribution of the vagi to raise a question as to the routine use of the abdominal approach especially for the occasional performer of vagotomy However the great advantage possessed by laparotomy in making possible detailed examination of the abdomen and of the ulcer as well as the frequent need for gastroenterostomy has gained for the abdominal approach a marked preference in the majority of clinics

Clinical Results—Relief of Pain —The most striking effect of vagotomy in an ulcer patient is the immediate relief of pain Since great emphasis is placed on this fact in all post-operative reports, it should be made clear that the same dramatic relief of ulcer pain is immediately obtained even in the most painful types of ulcer with high acid values and large volumes of continued nocturnal hypersecretion by medical measures which result in complete and continuous neutralization of the free hydrochloric acid content in the stomach throughout the day and night

As yet there is no unanimity of opinion as to the mechanism of the relief of pain by vagotomy Since the pain of ulcer is clearly an acid type

gastric ulcer to be approximately the same size as before operation and subtotal resection was done

The weight of opinion at the present time is that the operation should be done only in carefully selected cases There is general agreement however regarding the outstanding usefulness of vagotomy in cases of gastrojejunal ulcer The writer has seen very large gastrojejunal craters in individuals, who were debilitated and emaciated by noctural pain and inanition, disappear within a few weeks after transthoracic vagotomy with complete restoration of health in a few months time Resection in such cases frequently presents a serious surgical problem with relatively high mortality rate and with the risk of a subsequent gastrojejunal ulcer If future experience shows that vagotomy will prevent the occurrence of marginal ulcer and that gastrojejunal ulcer once healed by vagotomy does not recur after the return of gastric secretion to normal the operation will have justified itself on this score alone

Surgical opinion in general is against resort to vagotomy for ulcer of the stomach Gastric ulcer which fails to heal under careful medical management should be resected and examined histologically thus obviating the possibility of error with respect to malignancy

The major proportion of gastric neurectomies have been performed in cases of duodenal ulcer and the question which remains to be answered is whether the end results as observed over a period of years will show that vagotomy, with its almost negligible mortality rate is a better surgical procedure for refractory types of this lesion than the present operation of choice subtotal gastric resection, with its 85 per cent to 90 per cent of good results but with a somewhat higher mortality risk Difficulty in drawing conclusions will arise from the fact that there is an increasing tendency to combine vagotomy with gastroenterostomy even in non obstructive duodenal ulcer to lessen the possibility of troublesome gastric stasis Thus in the Miller and Olwin[100] series 56 of 101 patients were gastroenterostomized although 25 were non obstructive Since gastroenterostomy alone so commonly results in healing of duodenal ulcer with excellent operative results for a time it is obvious that a final evaluation of the benefits an ulcer patient may expect to derive from vagotomy must await observation over a period of years of a large series of cases in which section of the vagi will have been the sole surgical operation In the meantime total vagotomy as a surgical procedure in the treatment of gastric and duodenal ulcer must be considered to be in an experimental stage

of Massachusetts General Hospital vagotomy cases reported by Moore[99] 5 per cent had fullness and eructation continuing and still bothering the patient and 8 per cent had fullness with vomiting constituting a major problem detracting from the end result of the operation"

Diarrhea is a side-effect of equal or greater frequency Fortunately, it is also of temporary duration in most cases However, Miller and Olwin[100] found it to be the chief cause of trouble post-operatively as well as the most obstinate of the side effects, and Moore[99] reports that it was a major problem detracting from the end result in 6 per cent of the Massachusetts General Hospital cases

Thus it becomes clear that certain distressing digestive tract symptoms may persist after vagotomy The extent to which these troublesome side-effects will prove to be a definite hazard to be taken into account in advising for or against vagotomy will be known only after several years of observation Such a hazard exists in wide gastric resection following which a certain small percentage of patients have persistent low grade diarrhea nausea epigastric discomfort and failure to gain weight sequelae which have not been of sufficient frequency or seriousness however to invalidate the great usefulness of subtotal gastric resection which is still the operation of choice for recalcitrant peptic ulcer in the majority of the great surgical clinics in this country

Operative Results —Great diversity of opinion regarding the desirability of employing vagotomy in the treatment of ulcer has been expressed by surgeons who have had wide experience with the operation Dragstedt[101] stated that "the clinical results of the operation have been excellent and have led us to the impression that a benign peptic ulcer may be regularly expected to heal if all the vagus fibres to the stomach are divided On the other hand Walters and associates[102] found the results inconstant, variable and in most cases unpredictable" and cite cases to support this point of view among others a case with a large penetrating ulcer on the lesser curvature of the stomach just below the esophagus in which gastric resection would have been difficult After failing to secure healing from a period of medical treatment, transthoracic vagotomy was performed and the diaphrgm incised to permit a biopsy of the ulcer, which was found to be benign Within 3 weeks after vagotomy ulcer pain recurred, although the insulin test postponed until 2 months after the operation, was completely negative there being no free HCl with a hypoglycemia of 45 mgm Four months after vagotomy gastric analysis yield 26 units of free HCl, total acid 40 X ray showed the

Determination of the progress of healing of duodenal ulcer does not lend itself so readily to x ray study due to the fact that cicatricial contraction is an important element in causing the deformity of the duodenal cap, hence a certain degree of deformity is likely to persist even after all spasm and inflammatory swelling has disappeared and healing is complete When a definite duodenal crater has been visualized it is important to check the progress of treatment by noting the disappearance of the barium fleck evidencing the ulcer crater It is also important to make x ray observations at intervals for some weeks or months in cases in which it is necessary to observe whether or not a pyloric obstruction present when the patient was first placed on management has disappeared To make a final determination of the cicatrization of duodenal ulcer one must rely upon careful fluoroscopic examination of the ulcer area for the presence or absence of any degree of spasm or irritability of the cap If the deformed cap holds barium well and no irritability of the adjacent muscle wall is observed it is highly probable that the lesion is healed Thus while the length of time required for the treatment of duodenal ulcer will be governed in part by the degree of its chronicity the fluoroscope must be the final arbiter and no ulcer patient should be discharged as healed so long as evidences of inflammation in and about the duodenum are shown by the visualization of spasm and irritability of the cap

The chief cause for failure to obtain satisfactory results by medical measures is the tendency to modify too soon the strict regime employed in the early weeks of treatment by lengthening the period of time between feedings and decreasing the number of alkaline powders to be taken When such concessions to principle are made at the end of a few weeks of good treatment the patient may do very well for a time on the half way measures substituted but all too frequently the well remembered pain is once more in evidence after a variable lapse of time and another medical failure is recorded It is possible to secure to a remarkable degree the intelligent cooperation of ulcer patients in carrying out the details of treatment as described not only for some weeks but for many months, if demanded by the requirements of the individual case To obtain such cooperation it is necessary to inform the ulcer sufferer of the essential nature of his malady and of the various influences which may affect it for good or ill Intelligently informed regarding the rationale of the principle of acid control in the healing of ulcer as well as the need for adequate rest and recreation and care as to food and drink the average ulcer bearing individual is as willing to assume

Duration of Treatment

The length of time required for a peptic ulcer to heal depends upon its size depth the amount of induration in its walls and base, the extent to which the local blood supply has been blocked by thrombosis and cicatricial contraction and the completeness with which the various factors involved in the pathogenesis are removed or rendered inoperative Ulcer heals by granulation tissue formation and cicatrization as a result of the natural reparative processes inherent in vital tissues All that medical treatment can do to promote healing is to remove, so far as possible the causes and conditions that retard or prevent healing The great frequency with which the scars of healed ulcers are found in the stomach and duodenum at autopsy bears witness to the strongly inherent tendency of ulcer to heal, even without treatment A characteristic feature of the anamnesis in cases of chronic ulcer is the history of repeated remission of symptoms often for periods of many months Such remission periods suggest the likelihood of variable degrees of spontaneous healing of the lesion recurrently succeeded by exacerbation of destructive peptic action and accompanying inflammatory reaction

It has been shown by a study of the healing processes in gastric ulcer subjected to medical treatment for some weeks and then resected that under favorable conditions large ulcers may heal within 6 to 8 weeks time provided the lesion is of relatively recent origin Fortunately it is possible to observe with the fluoroscope the progress of healing in penetrating ulcers of the stomach, and the effectiveness of the medical measures used in a given case should be checked by x-ray examinations repeated every 10 days or 2 weeks until the defect disappears In the writer s experience gastric ulcers with certain relatively rare exceptions, disappear in so far as the x ray evidence is concerned in from 3 to 8 weeks The exceptions usually are large chronic ulcers of very long standing with thick callous base adherent to some adjacent structure such as the pancreas and with a limited blood supply Such ulcers may be difficult or impossible to heal and should be resected Disappearance of x ray evidence of the ulcer defect should not however, be taken as conclusive proof of complete healing of the lesion No deviation from the strictness of the treatment regime should be permitted for at least 2 months after the defect no longer can be visualized by radiological examination In other words even in the types of gastric ulcer most readily amenable to healing accurate medical treatment should be in effect for at least 3 months

hour after the mid day meal a powder is taken an hour later a glass of milk followed at three quarter hourly intervals by an alkaline powder for two doses In the evening three alkaline powders are taken at three quarter hour intervals This manner of partial acid neutralization prevents a high acid curve and may have some value in preventing recurrences The length of time this regime should be continued may be governed by conditions in the individual case Under no circumstances should this modified schedule be used as an effective form of treatment of an active ulcer A systematic, periodic inquiry into the patient s status either by personal interview or by letter such as is carried out in well organized diabetic clinics is of the greatest value in the protection it affords the individual with an ulcer diathesis Gastric ulcer patients should be fluoroscopied at intervals of some months for at least a year after healing has taken place

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responsibility for his future comfort and well being as is the sufferer from diabetes

Prevention of Recurrences

The difficult problem of safeguarding the patient against recurrence of ulcer after healing is one of primary importance The tendency of the lesion to recur either at the site of the ulcer cicatrix or in an entirely new area is too well recognized to require comment Recurrences take place after surgical operations whether by gastric resection, local excision or gastroenterostomy as well as following medical treatment (Fig 1) The responsibility of the physician is only in part discharged when healing of the lesion has been achieved The patient must be informed of the essential nature of the disease It must be made known to him that he has an inherent tendency to peptic ulcer formation and that, if he would avoid in so far as possible the discomforts and dangers of a reformation of ulcer, certain regulations should be observed Not only must all foci of infection in teeth, tonsils and sinuses be eradicated as a primary part of the treatment but the patient should be instructed to have the teeth examined and if necessary, x-rayed at stated intervals The very great importance of shielding the nervous system from periods of excessive stress and strain must be emphasized A minimum of 8 hours of sleep should be had and adequate vacation periods arranged If the type of employment in which an ulcer-bearing individual is engaged, is nervously exhausting, the possibility of a change of occupation should be explored

The experimental production of acute and subacute gastric ulcers in cats by the intramuscular injection of caffeine in beeswax (Roth and Ivy [7]) suggests that tea and coffee should be used sparingly Concentrated alcoholic drinks should be avoided and tobacco if used at all, should be used in moderation not because of any appreciable effect on gastrict acidity (Schnedorf and Ivy [8]) but because of its effect on the vasomotor system One must learn to eat slowly and masticate food thoroughly, avoiding highly seasoned spicy food, greasy substances and articles which are likely to be ingested in a coarse state of subdivision, such as nuts radishes cucumbers and raw cabbage

After the healing of an ulcer has been confirmed by final x ray examination the strict ulcer management may be modified in the following manner An alkaline powder is taken an hour after breakfast and an hour thereafter a glass of milk followed an hour later by a powder One

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CHAPTER IV

DISEASES OF THE INTESTINE AND SOME POORLY UNDERSTOOD DISTURBANCES OF DIGESTION

By Walter C. Alvarez, J. Arnold Bargen and Philip W. Brown

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Methods Used in the Diagnosis of Diseases of the Colon

Ordinarily in a case of colonic disease after the history is taken, the stools should be examined the rectum and sigmoid flexure should be studied with the sigmoidoscope and the colon should be visualized with a barium enema or with injected gas Because the presence of barium in the feces makes difficult the search for parasites and ova it is best first to study the stools, second to examine the rectum and last to make the necessary roentgenologic studies

In some cases of course the digital examination of the rectum, made when the patient is first seen will show the presence of a cancer, and then little more need be done in a diagnostic way Because metastasis from rectal cancer is often most pronounced in the liver much prognostic information can sometimes be obtained by doing a liver function test of the Rowntree Rosenthal type If this should show a high degree of dysfunction the probabilities are large that the liver is full of cancer cells and operation will be useless

Examination of the stools for occult blood should always be made before the sigmoidoscope is passed because the pressure of this instrument against the mucous membrane commonly causes a little bleeding

Examination of the Stool

In order to get some idea of the efficiency of a patient's mastication and digestion it is best to study first a sample of the usual stool passed in the morning In searching for parasites and ova and particularly for amebas it is best to take the second stool passed after the taking of a saline cathartic Naturally, the sooner this stool is studied after evacuation the better In many cases the patient must be asked to stop taking hydrocarbon oil because it is almost impossible to find ova or cysts in a stool full of this substance

Soft mushy or liquid stools are due either to catharsis or to the presence of diarrhea Hard formed stools or scybalous masses are associated with constipation Flattened, or ribbon like stools or stools of small caliber are commonly supposed to be due to a narrowing of the lumen of the sigmoid flexure or rectum,

but actually they are often due simply to a softening of the consistency of the fecal matter If anal bleeding can be excluded blood streaks on the stool or flecks of red blood suggest the presence of an ulcer or carcinoma in the colon

The normal brown color of the stool is changed when the following foods and drugs are ingested with milk the color is light yellow with cocoa and chocolate dark gray with blueberries and blackberries and Concord grapes dark brown or almost black with large doses of calomel or large portions of spinach green to dark green with iron and bismuth almost black and with beets occasionally red Clay-colored or putty like stools are seen when bile fails to enter the intestine Large amounts of blood coming from the upper portions of the gastro-intestinal tract give rise to black tar like sticky stools

Mucus is present in all stools in varying amounts Patients often bring to the physician long streamers of mucus

Round worms or segments of tapeworm may be found The smaller worms are searched for while the fecal matter is washed through a sieve with running water The material retained in the sieve should be floated out in clear water and examined in a thin layer in a flat bottomed dish placed over a dark back ground Examination with a hand lens may be necessary in order not to con fuse small worms with vegetable fibers or cells and shreds of mucus

In the chemical examination of the stool the most important procedure is the search for occult blood Often the test is of little value because it cannot be depended on in the making of a difficult diagnosis It must always be re membered that a positive reaction may be due to blood or leukocytes coming from the gums or elsewhere With all its limitations however a repeatedly positive blood test with guaiac will sometimes warn the clinician that he had better keep on looking for a carcinoma somewhere in the digestive tract It is usually stated that the patient should be on a meat free diet for twenty four hours before a stool is tested but if one wishes surely to avoid getting residues from a certain food one must wait at least four days before a stool is taken Actually many persons who are eating meat every day will not show occult blood in the stools even with the benzidin test

The estimation of the amount of pancreatic ferments in the stool is seldom helpful first because the pancreas has a large factor of safety in its functions and second because the rate of progress of the fecal residues through the bowel has a large influence on the amounts of pancreatic ferments that reach the anus

The microscopic examination of the stool gives additional information in regard to the efficiency or inefficiency of digestion and to the presence or absence of blood pus and particularly animal parasites and ova Ordinarily the presence of some meat fiber or starch grains in the stool has little if any significance

The presence of much neutral fat suggests the presence of pancreatic injury, obstruction of the common bile duct, or sprue

Endameba histolytica and Balantidium coli are the two protozoa that are surely pathogenic Several other parasites or their ova or cysts are commonly found in the stools but so far as is now known most of them have little if any power to produce disease

Bacteriology of the Stool — It would seem at first sight that bacteriologic examination of the stools should throw much light on many gastro intestinal upsets With such a large number of organisms many of them pathogenic, it would seem as if an overgrowth of one or other group ought to cause disease Actually although much has been written about maintaining a proper balance between proteolytic and saccharolytic floras, and many efforts have been made to change one type into the other our impression is that little that is definite or helpful has come out of it all

With so many organisms aerobic and anaerobic, present in the bowel the technic of really analyzing the situation in any particular stool is a difficult one and one that calls for much equipment and much skill After much work is done the investigator commonly will be disappointed at his inability to find any great difference between the bacteria of a normal stool and those in the discharges from a patient with diarrhea or with symptoms suggesting the presence of intestinal autointoxication

Usually all that the bacteriologist can do for the clinician puzzled over a case of diarrhea is to assure him of the presence or absence of organisms of the typhoid, dysentery or enteriditis groups He will also look particularly for the diplostreptococcus found by Bargen in so large a percentage of cases of chronic ulcerative colitis The technic for doing this has been described at length in the book on the colon by Rankin Bargen and Buie

In recent years efforts are being made to identify disease producing organisms in a patient s stools by isolating a number of them making antigens and then testing them on the skin Morris and Dorst found in this way that some invalids are highly skin sensitive to their own colon bacilli but their results obtained by injecting vaccines made from these organisms were not sufficiently encouraging Better results have been secured with the use of sodium ricinoleate given by mouth, but as yet little is known about the value of this drug

Proctoscopy and Sigmoidoscopy

It is easier to think of studying heart disease without the stethoscope than to think of attempting to diagnose affections of the rectum and distal colon without the help of the sigmoidoscope and the exploring finger and yet, when

faced by a patient who complains of bloody discharge from the rectum the average physician today seems to be satisfied with his ability to guess that the trouble is due to hemorrhoids or to dysentery As a result most of the patients who are found by the consultant to have ulcerative colitis have not received intelligent treatment, and, what is even more tragic, one out of five patients seen by us with carcinoma of the rectum has just come from the hands of some one who operated on him or her for the relief of hemorrhoids

Unfortunate also is the fact that many of the men who do use a proctoscope do not know a normal mucous membrane when they see it and as a result, they often frighten their patients unnecessarily with the diagnosis of colitis Others who do not use the anoscope commonly fail to recognize the presence of those small anal fissures which are so painful and troublesome to many patients Obviously the physician must either learn to use these instruments skillfully and routinely or else he must refer all patients with diarrhea and constipation and rectal pain or bleeding to one who is an expert in treating these conditions

Before the physician attempts to make a sigmoidoscopic examination he will ask the patient to take one or more enemas consisting of a small amount of warm physiologic saline solution Only occasionally is it desirable to examine the rectum without preparation as when cultures are to be made

The passage of the proctoscope should not cause pain unless there are cicatrizing lesions about the anus In that case a little 10 per cent solution of cocain may be painted on the anal ring The examination is best made with the patient upside down on a special proctologist s table but in the absence of this convenience the patient may be made to lie over the side of the bed with the head and shoulders on a pillow on the floor or he or she may be placed in the knee shoulder position Patients who are very ill will have to be examined in the Sims position

A digital examination of the rectum should always precede the passage of the proctoscope Simple inspection of the anus and digital examination usually will serve to disclose the commoner lesion such as fissure hemorrhoids kraurosis perirectal abscess or fistula inflammatory nodules due to the injection of hemorrhoids anal polyps hypertrophied anal papillæ and carcinoma of the rectum

With the sigmoidoscope the physician will see perhaps the pearly somewhat translucent normal rectal mucous membrane with blood vessels coursing through it he may see the granular easily bleeding mucous membrane with or without ulcers that is so characteristic of chronic ulcerative colitis or he may see the characteristic punched-out umbilicated ulcers of amebic colitis with normal mucous membrane in between The diffuse ragged type of ulcer due to tuberculosis is less distinctive The ulcers produced by Balantidium coli may resemble those of amebic colitis Rarely when radium has been used in the

vagina one will see a reddened, easily bleeding rectal mucous membrane which is streaked with newly formed blood vessels

Carcinoma of the rectum can easily be discovered with the finger and in all cases it should be recognized with the proctoscope Occasionally it may be advisable to remove a little piece of the tissue for microscopic examination and for the clearing up of any doubt that may remain as to the nature of the lesion A biopsy may be helpful also when it comes to convincing the patient or the relatives that a serious and very repugnant type of operation must be performed Sometimes also the microscopic sections will show such a highly malignant type of growth that it will seem unwise, especially in the face of other discouraging circumstances to attempt a radical operation

Swabbings from the mucous membrane of the rectum or from the floor of an ulcer often will be helpful, if they yield cultures of the diplococcus which is so commonly found in cases of chronic ulcerative colitis, or if they show the presence of amebæ or Balantidium coli

Roentgenologic Examination of the Bowel

Barium should never be given by mouth until the physician is satisfied that obstruction of the bowels is neither present nor imminent It can easily be seen that when there is a narrow place somewhere in the gut, the barium may accumulate above it and form there such a hard mass that it has to be dug out by the surgeon Obviously when this happens the risk of any operation is bound to be much greater than it otherwise would be It is not so dangerous to give an opaque enema because if a pronounced obstruction is found the flow of the liquid can immediately be stopped In many cases in which the obstruction is in the rectum the lesion can be discovered with the help of the finger and a roentgenologic examination then will be unnecessary

Unfortunately it is difficult to learn much about the condition of the small bowel with the help of a barium meal Sometimes signs of obstruction can be made out, but too often the physician must turn away baffled at his inability to learn anything about conditions in one of the most important parts of the body

It is otherwise with the colon where much can be learned particularly with the help of the opaque enema This should be watched as it runs in, and obstructions or irregularities in the wall of the bowel will then become apparent. The search for polyps and small carcinomas has been greatly facilitated since the introduction of the technic in which the bowel is filled with some gas immediately after the patient has voided the barium enema Air is generally used, but some sensitive patients are distressed by it and it might be better to use oxygen or carbon dioxide because these gases are so promptly absorbed When

the colon is filled with the gas and stereoscopic films are made polyps or small *growths often will stand out beautifully outlined by a thin film of barium*

It is important that the colon be thoroughly emptied before the opaque enema is run in If there is no contraindication the patient should take one or two ounces of castor oil in the afternoon previous to the examination In order that there be no residue in the cecum in the morning supper should not be taken but some breakfast is allowed In the morning enemas of warm saline solution should be taken until fecal material no longer comes away Naturally the presence of any gas or feces in the colon makes it hard for the roentgenologist to be sure of his findings Occasionally when some narrowing of the bowel, presumably due to spasm is seen it is well to have the patient return for another examination

The commonest diseases that are discovered *with the help of the barium* enema are carcinoma diverticulitis tuberculosis chronic ulcerative colitis and those few inflammatory processes outside of the bowel which encroach on its lumen The filling defect in cases of carcinoma is often annular but it may be irregular and due to a polypoid type of growth The narrowed part of the bowel can often be seen to be rigid and sharp borders to the lesion may be made out Often a mass can be felt corresponding to the filling defect

In diverticulitis the filling defect may resemble that of carcinoma but it usually involves a wider segment its outlines are usually more serrated, diverticula may be seen and there will be some tapering of the shoulders in the obstruction Often a mass is present but it usually lacks the indurated and knotty character of the one that is due to a carcinoma

Segments narrowed by chronic ulcerative colitis usually are rather long there will be a loss of haustration in the bowel and the walls of the canal will usually be smooth In a typical case of chronic ulcerative colitis the haustra are gone at least from the left half of the colon the diameter is lessened and the length of the bowel is shortened

Tuberculosis usually affects the cecum or the terminal coil of ileum The filling defect usually is irregular and corrugated in appearance and perhaps the barium is scattered over the surface of the cecum in little flecks A boggy mass may be felt The affected part of the bowel often is so irritable that the barium enema or the residues from the barium meal will not stay in it In the cases of hyperplastic tuberculosis of the ileum the lumen of the bowel is much narrowed and a mass may be felt *In a case of megacolon the outstanding feature is the* huge bowel with its smooth walls Amebic colitis will occasionally produce a roentgenologic picture which can be confused with that of chronic ulcerative colitis

Many roentgenologists are inclined to diagnose colitis whenever the patient is constipated or whenever he or she presents a colon which has deep haustra

tions and perhaps some small corrugations here and there in the walls Actually it does not seem right for us physicians to tell these patients that they have colitis because if one examines the colon with the sigmoidoscope or if one palpates and carefully examines the bowel at operation or necropsy one cannot find any sign of inflammation of the wall The ending "itis" signifies inflammation to most physicians today and for this reason it seems to us that the term colitis should be reserved for use only in those cases in which there is a definite, demonstrable inflammation of the wall of the colon

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P W B
W C A

Diarrhea in General

Persistent or recurrent diarrhea may or may not be a symptom of serious import but always its cause should be searched for with the greatest care and thoroughness It is true that some persons can have several stools a day for years without coming to serious harm but it is equally true that others, whose complaint at first hearing seems trivial are really suffering with so dangerous a disease as chronic ulcerative colitis or cancer of the rectum Because these serious possibilities are always present it is obvious that the conscientious physician must never dismiss a patient with diarrhea until he has made a thorough investigation of the digestive tract

For years it has been customary with many physicians to make a diagnosis of "intestinal flu It is possible that there is such a disease, but in the present state of medical knowledge it is questionable if this term should be used There is no doubt that some persons suffer with diarrhea and some form of digestive upset for a few days when they have a cold, but the mechanism of the disturbance is not known The main reason for mentioning 'intestinal flu" at this point is that this diagnosis is so commonly used as a substitute for knowledge Any consultant who sees many patients with carcinoma in various parts of the digestive tract and with such serious diseases as chronic ulcerative colitis, must be impressed by the number of patients whose first symptoms were

thought to be due to 'intestinal flu' Obviously the conscientious physician should never be satisfied with such a diagnosis and certainly he should not rest content with it when the patient fails to recover promptly

Unfortunately even when every laboratory aid is fully used it is not yet possible to make a real diagnosis in even half of the cases of diarrhea As Cabot pointed out years ago in too many instances a study of the stools fails to reveal parasites or abnormal bacteria a look through the sigmoidoscope shows a normal mucous membrane and a glance at the roentgenograms shows that *there is no defect anywhere in the shadow of the barium enema* If, then there is no sign of hyperthyroidism or achlorhydria, if the patient's tongue is normal, and his knee jerks are in good working order and if he fails to improve on a low residue or elimination type of diet the physician must either admit frankly that he has no idea what the cause is or he must fall back on such vague terms as enteritis or nervous diarrhea

Many years ago when Cabot studied the problem of adult diarrhea in the Bellevue Hospital in New York and the Massachusetts General Hospital in Boston, he first excluded all cases of typhoid and bacillary dysentery Six hundred and forty cases were left in which the following diagnoses were made

RELATIVE FREQUENCY OF THE COMMON CAUSES OF DIARRHEA IN ADULT

(Massachusetts General Hospital 1903 1912)

	Cause unknown	*Cause known*	*Total*
Acute enteritis	253	33	286
Chronic enteritis	147	11	158
Cancer of bowel		52	52
Pernicious anemia		34	34
Mucous colitis		32	32
Exophthalmic goiter		25	25
Nervous diarrhea		17	17
Tuberculosis of bowel		15	15
Amebic dysentery		14	14
Fat intolerance		[illegible]	
Total			640

Obviously the diagnosis of enteritis which was made so frequently is not entirely satisfactory because no one can say during the life of a patient whether or not there are lesions present in the mucous membrane of the small bowel Still less satisfaction can be found in the fact that in the 286 cases of supposed

enteritis there were only 31 (1 ? per cent), in which the cause was known Actually, in some of these cases the diagnosis was made only at the time of necropsy In the 158 cases of chronic enteritis, the cause was known in only 0 7 per cent

The reader in 1935 may say ' but these results represent the defective state of our knowledge before 1914 Today we can do much better Although doubtless there has been improvement it is nothing to brag about, and surprisingly little has been published in recent years that serves to throw much light on the problem In 1931, Brown reported an analysis of 100 cases of diarrhea in which the diagnosis was indeterminate His impression was that even in recent years a real cause for diarrhea is not found in two-thirds of the cases seen

It is interesting to note that in 1 out of 12 of Cabot s hospitalized patients with diarrhea the cause was cancer of the bowel The incidence of cancer can hardly be so great among office patients In 1 out of 19 the cause was pernicious anemia

Forty one out of 81 patients suffering with acute, apparently transient, diarrhea ascribed the trouble to some indiscretion in diet Unfortunately the patients impressions of this type are often of little value Ptomaine poisoning was a frequent diagnosis made by patients but today few physicians believe that ptomaines are commonly found even in spoiled foods Upsets due to food are more likely to be due to the presence of living bacteria

According to Cabot passive congestion of the mucous membrane of the bowel is rarely a cause of diarrhea Only 8 out of 88 patients with badly decompensated hearts suffered at any time with looseness of the bowels In 7 other cases of cardiac failure the intestine showed at death the lesions of a severe enteritis Strange to say in only one of them was there a history of diarrhea Among 13 patients with chronic nephritis dying with cardiac failure and passive congestion of all the organs only one suffered with diarrhea

A striking result of Cabot s studies was that even in the presence of demonstrable tuberculosis of the intestine complicating pulmonary disease, diarrhea was complained of in only one case in three In only 29 out of 100 cases of tuberculous enterocolitis studied at postmortem at Bellevue Hospital was diarrhea present Still more curious was the fact that diarrhea was nearly half as common in cases of pulmonary tuberculosis without intestinal lesions as in cases with lesions Thus in 160 cases of pulmonary tuberculosis studied post mortem, 14 per cent of the patients had suffered with diarrhea, although in them lesions could not be found anywhere in the bowel

In cases of cancer of the intestine 32 per cent of the patients at the Massachusetts General Hospital and 20 per cent at the Bellevue, suffered with diarrhea Contrary to the usually accepted idea on this subject, Cabot did not

find that diarrhea was any commoner in diseases involving the lower part of the colon than in those involving the upper part

Diarrhea of a supposedly compensatory nature is said to occur in cases of chronic renal disease and Cabot found evidence of it in 11 of 72 cases of chronic nephritis

Only 3 of 10 adult patients with intussusception complained of diarrhea

Sixty cases of colonic ulceration were collected at the Massachusetts General Hospital and 111 at Bellevue These are not all included in the 640 studied by Cabot It is surprising to learn that in more than half of the cases diarrhea was not complained of and the lesions were discovered accidentally at necropsy

In most cases of enteritis without diarrhea the diagnosis must be impossible Often there is no tenderness of the abdomen and nothing to indicate the presence of the disease This however is what one would expect from the fact that the intestinal ulcerations of typhoid fever and tuberculosis are much more likely to be associated with constipation than with diarrhea Thus in only 17 per cent of 1 495 cases of typhoid fever analyzed in Osler s Modern Medicine was diarrhea present although presumably in every case the intestinal wall was extensively ulcerated

Diarrhea was present in only 10 of 22 cases of mucous colitis in this disease the patient generally is constipated

If in a given case none of these common causes of diarrhea is found the physician can only suspect that some lesion is present that he cannot detect or that some function of the bowel has been upset Perhaps the gut has become too irritable and too responsive to every stimulus as in cases of hyperthyroidism or something may have gone wrong with the function of absorption or with the nervous mechanisms controlling peristalsis To show the depths of our ignorance we need only admit that in some cases the physician is no wiser after he has watched the necropsy on a patient who died of diarrhea

History Taking

The first thing to do in any case of diarrhea is to take a thorough and intelligently directed history This should be done in spite of the fact that the wise physician will never attempt to make a diagnosis from this history alone Too often it happens that the big game hunter who has just returned from a year in the jungles of India with amebic cysts in his stools is suffering with a carcinoma in the rectum or the patient who is recovering from tuberculosis has lesions typical of chronic ulcerative colitis

The physician will first want to make certain of what the patient means by the term diarrhea One individual may mean that he has one soft or watery

stool a day while another may mean that he has twenty or more stools Another will admit on questioning that in reality he is constipated, but that he is suffering with tenesmus or is having frequent small passages of bloody, purulent or mucoid material practically unmixed with feces The patient with exophthalmic goiter and diarrhea may have twelve or more perfectly formed stools a day due purely to the nervous overaction of the bowel

The next question will be when did the diarrhea first appear, and what were the events that seemed to be responsible for it? Did the first attack follow the eating of warmed over food at a picnic, or did it follow eating when the patient was much upset nervously or badly fatigued by travel? There is no question that in some persons fatigue or excitement or worry or annoyance or even mental preoccupation will so stop the digestive processes and so dry up the secretions that the normal breaking up of food into its chemical constituents fails to take place and diarrhea results During the process the mucous membrane of the bowel appears to be irritated the power of absorption fails, and if the sufferer goes on eating the usual amount of coarse foods, a vicious circle is started The fact that diarrhea is present one day makes it more difficult for efficient absorption to take place the next and so the process goes on Such a diarrhea can be stopped if the patient will avoid eating for a day or two and then begin again with small amounts of low residue foods

It is helpful to learn if the diarrhea has been constant, or if it has come in spells scattered over many years Not infrequently diarrhea alternates with constipation and in some of these cases a cure might be obtained if a sustained effort were made to remove impacted feces before they rot and produce irritation of the colon In many cases it is helpful to know that the patient has had tuberculosis or has been heavily exposed to it in youth In other cases it may be learned that the patient has an inherited tendency to looseness of the bowels and that he has had it off and on ever since childhood and youth He may confess that all through life even the amount of excitement attendant on the starting of a journey or the giving of a paper before a scientific association was sufficient to bring on diarrhea

It is customary to ask the patient if he ever lived in the tropics, because this does make it more probable that he is infested with amebas and other parasites Actually, however it must always be remembered that most places in the United States have a tropical climate during the summer, and even Alaska can be uncomfortably warm It must also be remembered that people can become infected with amebas anywhere A few years ago so many cases of acute diarrhea occurred among the guests at a large hotel in Chicago that the health authorities heard of it and soon discovered that the stools of one of the pantry men were swarming with cysts of Endameba dysenteriae When this man was discharged and active treatment instituted, the epidemic ceased

In occasional cases it is helpful to know that the diarrhea complained of occurs principally in the morning It may even wake the patient and get him out of bed every day at sun up There will often be one or two stools about breakfast time and after that the patient will be comfortable for the rest of the day Such morning diarrhea is sometimes associated with a lack of hydrochloric acid in the gastric juice

It is helpful to inquire if the diarrhea wakens the patient at night When it does the physician will strongly suspect the presence of some organic lesion such as chronic ulcerative colitis The so-called nervous or functional diarrheas are much less likely to disturb the patient s sleep

Severe tenesmus and an inability to restrain defecation for any length of time after the call comes point strongly to the presence of serious inflammation of the rectal mucosa or of a cancerous growth in that region The physician will want to know *how much pain is associated with the diarrhea* Colic and griping are more likely to be associated with acute attacks They may also be associated with diarrheas due to attempts on the part of the bowel to push on ward a polyp or a carcinoma There is often considerable aching and distress in the pelvis in cases of carcinoma of the rectum

It is always well to ask if the tongue is ever sore as it is in cases of sprue and pernicious anemia one must inquire al o about numbness in hands and legs and about relatives who may have died of anemia

Looseness of the bowels is apparently physiologic in many women at the time of menstruation As one would expect from this women patients with diarrhea due to ulcerative lesions of the colon are likely to be worse when they are menstruating

It may be helpful to learn that the diarrhea followed some abdominal opera tion In this case it may be due to a flareup in a previously unrecognized amebiasis or ulcerative colitis or if gastroenterostomy was done it may be due to a too rapid emptying of the stomach with the resultant jejunitis It may even be due to the formation of a gastro jejunal ulcer and later a gastro-jejuno-colic fistula When such a fistula is present unchanged food will appear in the feces shortly after it is eaten

Occasionally severe diarrhea following gastroenterostomy performed by a general practitioner will be due to the fact that a loop of ileum was inadvert ently connected with the stomach Occasionally also the patient will not know that the operation performed was an ileosigmoidostomy In every case in which there is doubt as to the nature of the operation done it is well to write to the surgeon for information

It is important to find out if at any time the patient was placed on a low residue diet and if so if this had any effect on the number of bowel movements If rest and proper diet have been well tried and found wanting the con ulting

physician will know that the disease is either refractory and possibly serious in nature or else that it is "*functional*" *Much then will depend on whether or* not weight has been lost

It is remarkable how few of the patients who come to the internist com plaining of chronic diarrhea have ever dieted to any extent or have made any attempt to restrict the amount of fruit and vegetables and other laxative foods eaten It is strange that even when these patients consult a physician, they are often advised to take larger amounts of the laxative foods, the idea apparently being that they should have more vitamines Actually if the use of vitamines *had been indicated they could have been given in concentrated form*

It is helpful to learn more details of the treatment received by the patient from other physicians If the usual astringent drugs have had no effect, the chances are that the disease will be somewhat refractory It is important also to know if parasites have been looked for or found by competent laboratory workers If the endameba of dysentery has been found the physician will want to know what treatment was given, and how successful it was in removing the cysts If they disappeared for a time was there any concomitant improvement in symptoms?

The physician will ask in regard to the appearance and consistency of the stools and particularly as to the presence of blood and pus and mucus He *will want to know about the bulkiness of the stools, their fat content, their* color their odor their frothiness and their content of undigested food

After taking the history and making a complete physical examination the physician will want to examine the stools he will want to make a proctoscopic and sigmoidoscopic examination and he will want a roentgenologist to observe the passage of a barium enema through the colon When all this work has been done most of the serious diseases of the colon, such as ulcerative colitis, cancer, amebiasis, polyposis tuberculosis and diverticulitis will have been recognized Unfortunately as was pointed out early in this section, there will still remain a large group of cases in which the cause for the loose movements cannot be determined with certainty

In Brown s series of 100 cases *there were 31 patients with one or more types* of parasite in the stools A successful effort was made to remove the invader, at least temporarily in every case of infestation with Endameba histolytica and Giardia lamblia *but the failure to get any improvement in the symptoms made* it seem probable that the cause of the trouble had not yet been found There were reasons for believing that in 4 cases the diarrhea was neurogenic in origin, in 6 it may have been reflex to disease in other organs in 31 it seemed to be due to an irritable bowel, whatever that is in 18 it may have been due to an allergic type of sensitiveness to food in 7 it followed an acute infection of some kind, in 19 it was thought to be due to a deficiency in diet, in 13 the clinical

picture resembled that of sprue and in 2 the most striking symptom was a defect in the digestion of fat

Treatment of Diarrhea

Acute Diarrhea — In the case of acute diarrhea, the objectives usually in the mind of the physician are first to clean out if necessary any irritant materials which may be left in the digestive tract, second to give the bowel as much rest as possible third to quiet its excessive irritability and fourth with the help of some inert powder to solidify the feces and thereby stop the growth of harmful bacteria

Many physicians begin the treatment of diarrhea by giving a dose of some purgative Actually in most cases in which the patient has already had several watery movements it would seem as if the bowel must be empty and that the giving of castor oil can only add insult to injury The essential thing is that *the oil be not given thoughtlessly and routinely Actually in scores of cases we* have seen, the symptoms subside promptly without the help of any purgative Occasionally the giving of an enema of warm physiologic saline solution will bring comfort to the patient and will give him rest

In most cases the patient will do well to go without eating for at least eighteen hours Water usually can be given by mouth or in the rarer choleraic types of diarrhea it will have to be given under the skin or by the veins It is most important to give the mucous membrane of the bowel a little rest because immediately after the insult by bacteria or irritating food there seems to be a failure of absorption which lasts for at least twenty four hours If during this time more food is given and particularly an excessive amount of food the mucous membrane is still further injured and a vicious circle is started Such a circle can be broken only by a short fast or perhaps by a reduction in the amount of food taken

After the bowel has been given a few hours in which to recover it is well to have the patient begin eating small amounts of those low residue foods which are usually given during the preparation of patients for operations on the colon The list will be found *in this chapter in the section on carcinoma of the colon* Ordinarily the best foods are beef mutton rice broths crisp toast tea coffee, jello and cooked eggs If these agree and the diarrhea stops the patient should then add potato pureed vegetables custards simple puddings and stewed fruits Ordinarily a normal diet can be resumed within a week

Most physicians are inclined to order milk for patients with diarrhea but this is not advisable because even when it is boiled it leaves a large residue in the bowel and besides there are many persons who get bilious when they drink milk.

In all cases of acute and severe diarrhea, rest in bed constitutes excellent treatment It helps greatly in quieting the bowel and in stopping peristalsis It may be helpful to give small doses of opium or codein to quiet tenesmus A commonly used drug is camphorated tincture of opium which can be given in dram (4 c c) doses Only enough should be given to relieve cramping and tenesmus

It is hard to say how much good the various inert powders do Sometimes the giving of bismuth subgallate tanalbin, tannigen or kaolin seems to help considerably Some of these drugs have an astringent effect, and others work probably by drying the stools and making it impossible for bacteria to grow actively in them In some cases it is possible also that bismuth helps by combining with the hydrogen sulfide that is formed in the colon

In many cases of acute diarrhea the difficulty comes in getting the patient back to regular intestinal habits Naturally after the gut has been thoroughly cleaned out and after the patient has been on a low residue diet, there is little fecal material to come away and regular bowel movements cannot be expected The patient who does not think of this begins to worry about the onset of constipation he takes a dose of some purgative and the diarrhea comes back Occasionally one will see a patient who for weeks has seesawed back and forth in this way between constipation and diarrhea Usually all one has to do to straighten out these people is to have them increase the amount of bulk in the stool and to take enemas of physiologic saline solution until the bowel is moving of itself again In some cases the patient goes back too soon to a rough diet and thus brings on the diarrhea again

Chronic Diarrhea — If possible the first thing to do in a case of chronic diarrhea is to make a diagnosis and to find a cause If this cannot be done, at least certain general principles can be followed In the first place, one should put the patient on a constipating type of diet with as little residue as possible Strange to say most physicians seem to be willing to treat patients with diarrhea without paying much if any attention to the diet Many depend entirely on the giving of bismuth and opium

The low residue diet will be described further on in the section on carcinoma of the colon After the diarrhea has quieted down a smooth diet should be adhered to for some time The length of this period of careful eating will have to depend largely on the severity of the diarrhea and the tendency which it shows either to terminate or to continue Laxative foods such as fruits vegetables and salads should be taken only after it seems clear that the disease has been cured It must not be forgotten however that in those cases in which the disease shows a tendency to run on for months the diet must be generous enough and complete enough so that nutrition will be maintained and deficiency diseases such as scurvy and pellagra will be prevented The various vitamines can always be

supplied in concentrated form fruit juices can be taken every day and calcium and iron can be supplied in the form of pills

In some cases in which the diarrhea is due to some particular food or foods the methods described in the section on food sensitiveness will have to be tried

In cases in which the main difficulty seems to be a failure in the dige tion of fat, the patient may improve a great deal on a diet that is poor in fat fairly high in protein and rich in carbohydrate

In the cases in which the patient has for some time been on a deficient diet it may help to give liver liver extract or ventriculin In these patients the carbohydrate allowance may have to be kept low for a while

Colonic irrigations should not be used routinely in the handling of patients with diarrhea In some cases however the giving of an enema of warm physiologic saline solution especially at bedtime will help in allowing the patient to get to sleep Just as in the case of patients with acute diarrhea the return to health is often dependent on the skill with which constipation or what is thought to be constipation is overcome after the diarrhea ceases The use of a purgative should be avoided like the plague because so often it brings on another attack of diarrhea

Just as in the case of acute diarrhea rest in bed is often very helpful in instituting a cure Occasionally nothing can be accomplished so long as the patient is being worried or upset by some annoyance at home or at the office In other cases measures that help to build up the patient s general health and resistance will be most helpful and a vacation in the country with sun baths will be more useful than a quart of medicine

Drugs are not always so helpful as one wishes they would be There are some patients with diarrhea who promptly respond to a little treatment but there are others in whom nothing seems to do any good Among the inert powders bismuth subgallate chalk and kaolin are perhaps the most useful Tincture of belladonna is of doubtful value and is not to be recommended

It is hard to say why the giving of calcium helps some patients Probably the most pleasant form in which it can be administered is the gluconate and several tablets can be chewed up and swallowed three hours after each meal

Many physicians attempt to disinfect the digestive tract with the help of drugs such as salol and magnesium salicylate There are many proprietary intestinal disinfectants on the market but there is little evidence to show that any of them do what they are supposed to do One of the latest products is dihydranol[3] which may perhaps be of some value It can be given three times a day with meals in a capsule containing 0 15 gm suspended in olive oil

In every puzzling and refractory case of diarrhea it is well to try a few doses of emetin hydrochloride given hypodermically and a few tablets of treparsol given by mouth If a dozen treparsol tablets given in the course of four days

do not produce any alleviation of the symptoms, the chances are that the disease is not due to an infestation with Endameba histolytica

Tincture of iodine given after meals in 10-drop doses well diluted helps in an occasional case and sometimes is worth trying It should be given for a week at a time and then discontinued for another week

Sedative drugs of the barbital type are often helpful in the management of chronic diarrhea The patient is treated much as if he had epilepsy or migraine and twice a day the nervous system is quieted with the help of perhaps 45 mgm ($\frac{3}{4}$ grain) of phenobarbital

When anemia is present iron containing food can be given, or the iron can be given in the form of Blaud s pills or ferric citrate Sodium ricinoleate has been used by Dorst and Morris[3] in cases of diarrhea in which allergic responses to food or bacteria were suspected The value of the drug cannot yet be estimated The encouraging fact about it is that in vitro it detoxifies bacteria and changes them in some way so that the body is no longer sensitive to them

For years attempts have been made to change the intestinal flora in patients with chronic diarrhea but as yet it is questionable how much good has been done In many cases the most careful study of the stools by expert bacteriologists fails to show any decided deviation from normal in the flora, and even when some abnormality can be shown it is hard to change conditions back to normal or what is thought to be normal, and it is still more difficult to maintain conditions as we think they should be Ordinarily physicians give commercial cultures of Bacillus acidophilus but unfortunately, some of these are not up to standard and most of the bacteria are dead In attempting to implant an acidophilic bacillus in the bowel it helps to give lactose, but the studies of Childrey, Alvarez and Mann indicate that lactose in fair sized dosage interferes considerably with the absorption of food and tends to act as a laxative

In an occasional case of chronic diarrhea and especially of the type in which the disease proves refractory to diet and inert powders, a sudden and miraculous cure can be obtained by injecting intramuscularly a little foreign protein such as typhoid vaccine If the desired effect does not follow the first dose it is not likely to be obtained with subsequent ones The good result will sometimes last for months

Further details in regard to the treatment of chronic diarrhea will be found in the section on chronic ulcerative colitis

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P W B
W C A

Enteritis in the Small Bowel

It is unfortunate for the clinician that as yet it is practically impossible for him to get an idea of the condition of that most important portion of the digestive tract the small intestine Here is an enormous surface of mucous membrane which not only supplies an important digestive juice but is responsible for practically all of the absorption of food which takes place in the body and yet we physicians have no way in which to estimate its functional capacity or to diagnose the presence of inflamed areas The barium meal goes through this segment of bowel so rapidly that small areas of inflammation or irritation are almost certain to be missed and even tumors are hard to find until they produce serious obstruction

It seems highly probable that at times there is some inflammation of this membrane and there is every reason to believe that such inflammation can be responsible for some of the acute and chronic upsets in digestion that are now thought to be functional in origin Unfortunately for the diagnostician enteritis in both small and large bowel is not always associated with diarrhea when it is discovered at necropsy usually it is hard to get a history such as one would expect to go with it It seems probable however that an undetectable enteritis can account for some of those many cases of diarrhea in which at present no cause can be found Some of the transient disturbances in the functions of stomach and bowel which so commonly accompany colds or other generalized infections may also be due to a mild degree of enteritis The studies of Childrey Alvarez and Mann indicate that the digestive upsets that follow the eating of too much food or of indigestible food may well be due to injury wrought to the absorptive power of the mucous membrane of the small bowel

Common causes for transient enteritis may be the toxins of the typhoid dysentery and enteriditis groups of bacteria Bacteriologists have tried to incriminate also the staphylococcus aureus and some of the streptococci

The diarrhea seen with poisoning by such substances as mercury and arsenic is probably due to an enteritis Enteritis appears also in the terminal stages of diseases such as portal cirrhosis carcinomatosis and nephritis The treatment of enteritis is that of acute or chronic diarrhea and this has been described elsewhere in this chapter

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W C A

DIARRHEA DUE TO INTESTINAL PARASITES

A complete discussion of the various parasites which infest the intestinal tract will be found elsewhere (see also Chapters XXXIII, XXXVIII, XXXIX, XLI and XLII in Vol V In this section we will give briefly only such information as is necessary to an understanding of some of the problems of diarrhea

Endameba Histolytica — In this connection the most important of all the parasites is Endameba histolytica (see also Chapter XXXIII in Vol V) As is well known, in the chronic form of infestation so commonly seen in the United States of America the patient does not complain of diarrhea and often he is even constipated Occasionally however there may be flare ups of diarrhea and sometimes even a bloody dysentery which can cause death Only rarely in the temperate zone will liver abscesses be found and very rarely a brain abscess Such abscesses will form sometimes in patients who have not suffered with diarrhea

The diagnosis depends on the identification of the characteristic cysts or parasites in the stools or in swabbings obtained on sigmoidoscopic examination In those cases in which the disease is active and the lesions plentiful the examiner can see through the sigmoidoscope punched out ulcers with normal mucous membrane in between Examination with a barium enema is not likely to show the scarring and narrowing of the colon which are so characteristic of chronic ulcerative colitis Only in rare cases will the differential diagnosis be difficult

When amebic cysts have been found in the stool, it is most important to remember that their presence may have nothing to do with the symptoms complained of by the patient these may be due to some other cause not yet recognized

Until a few years ago the treatment of amebic colitis was a drastic procedure which occasionally reduced the patient to a state of physical or financial exhaustion It included hospitalization intravenous injections of salvarsan and violent purgation due to the use of large doses of bismuth emetin iodide Such treatment is no longer necessary now that the cysts can promptly be driven

from the stools with a few doses of comparatively harmless drugs given by mouth It is true that in some cases reinfection occurs after a few months, but that happened also after the most drastic forms of treatment

One helpful feature of the mild types of treatment is that they give the physician a chance to see whether or not any benefit follows from the destruction of most of the parasites Unfortunately in many cases the enthusiastic specialist in tropical diseases is inclined to assume as self-evident that a long train of neurasthenic symptoms must be attributable to the presence of a few amebic cysts in the stool When as commonly happens a course of emetin and arsenic fails to give any relief his only thought is that the treatment has not been drastic enough and that it must be repeated In such cases a clinician of wider experience will be much more inclined to the view that the few parasites in the colon had nothing to do with the troubles If they had had their almost complete destruction should have led to some improvement in the symptoms an improvement which should have lasted until a new crop of parasites appeared

At the Mayo Clinic a patient with acute symptoms of amebiasis is given injections of from $\frac{2}{3}$ to 1 grain (0 04 to 0 06 gm) of emetin hydrochlorid twice a day for three days Another similar course is given a week later When active lesions are present and when the patient is suffering with diarrhea there is nothing that works so well as emetin Relief of symptoms is generally prompt but unfortunately, in over half the cases the drug fails to destroy all of the parasites For this reason in chronic cases or in patients who have just been relieved of acute symptoms with the help of emetin it is customary to give a short course of treparsol The dosage is 1 tablet containing 0 25 gm three times a day for four days Two or three more such courses may be given at intervals of from 8 to 10 days

Symptoms of intolerance to emetin or to arsenic must be watched for and on the slightest sign of toxic erythema dermatitis severe diarrhea, or neuritis the use of the drugs must be stopped It is probably unwise ever to attempt the giving of the substances a second time to patients who have shown that they cannot tolerate them It is a curious fact that whereas in some patients the giving of a few tablets of an arsenical drug such as treparsol will promptly produce damage to the liver or skin in others many times the usual dose can be taken at frequent intervals for years

Both emetin and treparsol can produce peripheral neuritis and perhaps also injury to the heart Patients who do not tolerate these drugs can be given yatren (anayodin) This iodin-containing substance is given by mouth in doses of 3 grams a day for seven days Two or more such courses are given at intervals of a week The drug may also be given well diluted in enemas that are to be retained Because yatren frequently produces some nausea and

diarrhea, the dosage may have to be adjusted to the idiosyncrasies of the individual

Balantidium Coli — This ciliate (see also Chapter XLII, Vol V), a common parasite of the pig only rarely attacks man Logan reported four cases in which there was an invasion of the mucous membrane of the bowel and the production of ulcers similar to those of amebiasis The disease may be acute or chronic In the acute stages it produces dysentery If this is recovered from a chronic form of the disease may follow in which the diarrhea is likely to be replaced by constipation Occasionally there is perforation of the intestinal wall with resulting peritonitis The prognosis in the acute type of the disease is grave In Logan s cases the disease was chronic and associated with a destruction of the blood similar to that seen in pernicious anemia The diagnosis can be established by the identification of the parasite in the stools or in material taken from the floor of an ulcer

The treatment so far has been unsatisfactory in one of Logan s cases a cure was obtained by giving each week intravenous injections of arsphenamine and on alternate days retention enemas of vinegar and tannic acid Unfortunately, although the parasite was eradicated and the diarrhea was controlled, the anemia was not relieved Cort has recommended the use of retention enemas of 150 c c of olive oil containing 15 c c of oil of chenopodium

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P W B
W C A

DIARRHEA ASSOCIATED WITH ACHLORHYDRIA

The student may gain the impression from some of his teachers and books that achlorhydria is a common cause of diarrhea but actually now it not only appears to be one of the infrequent causes but it becomes more and more obvious that there are hundreds of thousands of elderly people abroad in the land who are in good health in spite of the fact that they have no free acid in the gastric juice Vanzant and others have shown that the incidence of achlorhydria in persons who have little if any complaint to make about their health

and no demonstrable organic disease increases from 4 per cent at the age of 20 years to 26 per cent at the age of 60 years

Among 100 persons with achlorhydria Eggleston found only 8 with diarrhea In another series of 100 unselected cases of achlorhydria studied by Magath and Brown 18 of the patients complained of diarrhea and of these only a few were benefited by taking acid As yet no one knows why some of the patients with achlorhydria have diarrhea or why some of these are benefited by the taking of acid

It is known that food tends to pour out of the achylic stomach and this sudden dumping of undigested material into the duodenum could easily account for irritation and over activity of the bowel It is not so easy to explain why the symptoms commonly appear in the morning before or immediately after breakfast and are less troublesome during the rest of the day One explanation offered by Alvarez is that the bowel is rested during the night so that in the morning it is more sensitive and the reflexes are on a sort of hair trigger

Another explanation for the diarrhea is that it is due to irritation of the small bowel by bacteria which are not normally destroyed in the stomach by the acid Against this theory is the fact that in necropsies on patients with pernicious anemia one does not find any signs of inflammation in the intestinal mucous membrane unless the patient has survived for a long time in a much weakened condition

Achlorhydria has been thought to favor also the growth of intestinal parasites and particularly of the flagellates but this does not appear to be the case because Magath and Brown have shown that in only 11 3 per cent of 67 cases of Giardiasis and in only 10 per cent of 420 cases of infestation with Chilomastix mesnili and Trichomonas hominis was achlorhydria present It is conceivable that the absence of the acid may bring about some deleterious change in the intestinal flora but as yet no one knows what this change is

There is no doubt that achlorhydria is compatible with good health When diarrhea is found in association with it it is well to try the effect of dilute hydrochloric acid in a dose of about 30 minims (not drops) (2 c c) to be taken in one or more large glasses of water *with the meal* Some patients like to add some orange or lemon juice and some sugar With the idea of saving the teeth the drug may be taken through a glass tube and the teeth should be rinsed afterwards Complete destruction of the enamel on the lingual surface of the upper incisors has been observed in patients who for some time have been taking acid There are drugs such as acidulin (Lilly) which can be taken in capsule form the material in one capsule is said to form 10 minims of dilute HCl in the stomach

If the diarrhea is ever going to be controlled by the giving of acid improve

diarrhea, the dosage may have to be adjusted to the idiosyncrasies of the individual

Balantidium Coli — This ciliate (see also Chapter XLII, Vol V), a common parasite of the pig, only rarely attacks man Logan reported four cases in which there was an invasion of the mucous membrane of the bowel and the production of ulcers similar to those of amebiasis The disease may be acute or chronic In the acute stages it produces dysentery If this is recovered from a chronic form of the disease may follow in which the diarrhea is likely to be replaced by constipation Occasionally there is perforation of the intestinal wall with resulting peritonitis The prognosis in the acute type of the disease is grave In Logan s cases the disease was chronic and associated with a destruction of the blood similar to that seen in pernicious anemia The diagnosis can be established by the identification of the parasite in the stools or in material taken from the floor of an ulcer

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P W B
W C A

Diarrhea Associated with Achlorhydria

The student may gain the impression from some of his teachers and books that achlorhydria is a common cause of diarrhea but actually now it not only appears to be one of the infrequent causes but it becomes more and more obvious that there are hundreds of thousands of elderly people abroad in the land who are in good health in spite of the fact that they have no free acid in the gastric juice Vanzant and others have shown that the incidence of achlorhydria in persons who have little if any complaint to make about their health

In the acute gastro-intestinal crise of hyperthyroidism it is not always easy for the patient to retain the iodine that is so necessary if relief is to be obtained In such cases Haines adds from 4 to 8 c c of compound solution of iodine to 40 c c of water or grape juice and every few minutes a nurse puts or 3 drops of this in the patient s mouth In this way enough iodine is generally gotten into the body to give prompt relief Possibly the recently suggested technic of having the patient inhale ethyl iodide vapor might work well in these cases Tablets of lipoiodine Ciba, might also be chewed and swallowed without water

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P W B
W C A

CHRONIC ULCERATIVE COLITIS

Chronic ulcerative colitis is one of the most serious disease that can attack the digestive tract of man The only fortunate feature about it i that it is relatively uncommon The term colitis ulcerosa gravis which is used in Germany is somewhat more descriptive than ours in that it carries a reminder of the fact that the disease often has a fatal outcome The designation ' chronic ulcerative colitis of bacterial origin would be more complete and descriptive

Most of our knowledge in regard to the disease has been secured in the last decade It was mentioned by Wilks and Moxon[5] as early a 1875, and a colored drawing by Cruveilhier inserted in a paper written between 1829 and 1842 shows le ions that look like those that we see today Allchin showed a typical pecimen before the London Pathological Society in 1885 and called attention to the features which in his opinion distingui h the disease as an entity White gave another good account of the condit on in 1888 but the medical world paid little attention to the subject until 1919 when Logan[7] published his vivid de scription together with a careful statistical study of 117 cases This paper awakened the interest particularly of the American members of the medical profession and left no doubt in the minds of students of the disease that it con titutes an entity

ment should be observed almost immediately Occasionally the drug seems to bother the patient and then its use must be discontinued

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P W B
W C A

DIARRHEA DUE TO HYPERTHYROIDISM

Diarrhea is not an uncommon symptom of hyperthyroidism, and it may even be the chief manifestation of the disease in its early and more confusing stages It is usually seen with exophthalmic goiter and rarely with toxic adenomas W A Plummer obtained a history of diarrhea in 32 per cent of 579 cases of exophthalmic goiter in which the history was complete in regard to the condition of the bowels Ten years later he obtained a history of diarrhea in 27 per cent of 1377 cases In compiling these figures care was not taken to exclude diarrhea due to other diseases Brams found a history of diarrhea in 17 per cent of 1 5 cases of hyperthyroidism

Although hyperthyroidism may be present in a patient with diarrhea, the clinician who finds a high basal metabolic rate must not jump to the conclusion that his diagnostic problems are solved Particularly is this true when the diarrhea persists in spite of the giving of iodine because this will put a stop, usually very promptly, to symptoms that are due to hyperthyroidism

In the crises of hyperthyroidism and especially in those cases in which there is no obvious exophthalmos or enlargement of the thyroid gland one sometimes sees attacks of violent vomiting or diarrhea or of both symptoms combined So far as is known these attacks are not associated with any visible change in the mucous membrane of the bowel and hence all of the usual studies which can be made of the colon and stools of such a patient will fail to show anything wrong The mechanism that is responsible for the diarrhea is not known but it would seem to be either hormonic or nervous in character In some cases it should be noted that the trouble is not a true diarrhea but simply an increased frequency in the evacuation of feces that are well formed

isolated from the rectal lesions or stools in about 80 per cent of the patients studied (Fig 1) It has been found in foci of infection distant from the colon and it has been isolated from the blood of patients seriously ill with the febrile form of the disease and from the heart blood after death Also it has been demonstrated in and about the ulcers excised at necropsy Furthermore colonic lesions similar in every way to those in the intestine of man have been produced in rabbits and dogs by injecting intravenously cultures of this diplo-streptococcus

These observations have now been confirmed by Wendkos Soper Chisholm Torrey Portis DeBere Garrett Horgan and Horgan Streicher and Kaplan, Fradkin and Gray Lynch Rouse Kracke Sumont and Buttioux, Muniz De benedetti, Crohn and many others There would seem to be little question then about the fact of the close association of a particular streptococcus with the disease

The next questions are Is this diplo-streptococcus the only cause of chronic ulcerative colitis is there only one type of the disease and is the organism ever found in the feces of normal persons? Since the clinical picture usually is so characteristic and typical my colleagues and I were first inclined to the view that it has one cause and that when in the occasional patient we were unable to find the diplo-streptococcus it was because our technic had failed or because the organism was over grown by other bacteria Soon however we encountered cases in which it seemed more probable that other bacteria were the cause of the disease Thus there were cases in which the symptoms did not respond favorably after the injection into the patient of an antiserum made by im munizing horses to the diplo-streptococcus and in some of these at death another organism was found in the heart s blood These observations of course did not prove that the diplo-streptococcus was not the original cause of the disease because as every bacteriologist knows many organisms can get into the tissues and blood of a slowly dying patient

Streicher and Kaplan believe that other bacterial invaders are responsible for the disease in all of that 20 per cent of cases in which the diplo-strepto coccus cannot yet be found These bacteria might be other forms of strepto cocci or they might be diphtheroid bacilli staphylococcus albus aureus or hemolyticu bacillus pyocyaneus bacillus lactis aerogenes or bacillus coli The truth or falsity of this view will have to be established by future work A few writers continue to feel doubtful about the significance of the diplo-strepto coccus because they have been able to find it in only a small percentage of cases This is understandable when one remembers how difficult it often is to isolate any one bacterium from the enormous number in the bowel Even a little variation in technic can make the difference between success and failure Some workers may have failed also because they did not take material as they should have done from typical ulcers seen through the proctoscope

Etiology

Jex Blake and Higgs were the first in 1909 to speak of the disease as being of bacterial origin They considered as possible causes, Escherichia coli, Bacillus proteus vulgaris Bacillus pyocyaneus, Bacillus pyocaneus (Pseudomonas æruginosa) and streptococci In the fifteen years that followed, most workers looked upon these and other common intestinal bacteria as possible causes of the disease Among them were Wallis, White, Bassler, Hewitt and Howard, Strauss Lockhart Mummery, Yeomans, Rolleston, Hewes Stone, Strauss,

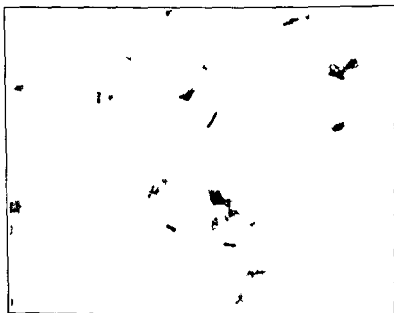


FIG 1 Diplo streptococcus isolated from rectal lesions and stools in about 80 per cent. of patients with chronic ulcerative colitis Magnified 1000 diameters

Friedman and Block Another group of workers among whom may be mentioned Hurst Thorlakson Leusden and Einhorn held to the idea that chronic ulcerative colitis is a sequel of bacillary dysentery For a time a number of writers thought of it as resulting possibly from some metabolic disturbance, but most of them have now gone over to the camp of those who believe in an infectious cause

My own studies[1], begun in 1923 and now including clinical and bacteriological observations on more than 1 000 patients with the disease, have convinced me that it is due to an infection in which streptococci of a certain type play the most important role A diplo-streptococcus closely resembling the pneumococcus and with definite morphologic and biologic properties, has been

cure in most of those cases in which the colon was not hopelessly damaged or in which the patient was not badly toxic and feverish

Perhaps the best proof of the causal relationship of the diplo-streptococcus to the disease is to be found in the fact that an antiserum prepared by inoculating horses with the organism has for some time now been working well even in the most severe forms of the disease

It seems significant also that at the Mayo Clinic, in the days *before the* use of vaccine and serum many ileostomies were made while since the introduction of the new treatment few have been necessary Incidentally the mortality *from this operation has been lowered because now it is performed not* as a last desperate venture when the patient is almost moribund but as a measure of relief for some sequela which has appeared after the lesions have largely healed

Attacks of chronic ulcerative colitis and recurrences of symptoms often follow acute infections of the respiratory tract such as bronchitis tonsillitis rhinitis influenza and pneumonia Exacerbations of the disease or reappearances after apparent healing seem to be caused at times also by over-exertion and fatigue Similarly the severe abdominal jarring that farmers get when driving a lumber wagon or tractor or when plowing has sometimes caused the disease to flare up

So far as is now known, the race and build of the patient and his dietary habits have little bearing on the incidence of the disease

Pathology

The lesions can be studied through the sigmoidoscope during the life of the patient or at the necropsy table after death Chronic ulcerative colitis seems often to pass through several stages Early in the disease there is hyperemia of the colonic mucous membrane *then edema followed by or associated with* miliary abscesses and finally miliary ulcers The picture as seen through the sigmoidoscope even in the early and mild cases is characteristic the mucous membrane is slightly hyperemic it bleeds easily and it has a finely granular appearance as if it had been glazed with melted but still somewhat crystalline sugar

The miliary abscesses, by a process of confluence and necrosis open out into shaggy ulcers which are separated by islands and peninsulas of mucous membrane This membrane retains its typically granular appearance and its tendency to bleed when touched with the proctoscope The last stage of the disease is the one seen at necropsy The inflammatory process is then diffuse and it affects all layers of the bowel All of them are thickened due to the replacement of the normal cell with extensive granulation and fibrous tissue

One of the best bits of evidence to show the etiologic relationship of the diplo streptococcus to the disease is that the organism has been found in pure culture in the small abscesses which form sometimes in the mucosa of the ileum after the operation of ileostomy They have been found also in the thrombi that sometimes plug the veins in the mesentery of the colon

Brown and Paulson remain the staunchest opponents of the view that the cause of the disease has been found They do not feel that the condition is an entity but rather that it can be produced in many ways In their small series of cases they did not always succeed in obtaining the diplo-streptococcus

The best answer to all such objectors would seem to be that it was to be expected that ulcerative colitis would at times be produced by organisms other than the peculiar diplo-streptococcus that is so commonly found in the lesions One has only to remember that all cases of pneumonia are not due to the pneumococcus to realize that similarly all cases of chronic ulcerative colitis need not be due to one streptococcus The pneumococcus is usually thought of as the cause of pneumonia because it is found present in the lesions in so large a percentage of the cases Similarly when one organism can be cultured from the lesions of 800 out of 1000 cases of chronic ulcerative colitis, it would seem as if the medical profession might, with justification feel that the cause of the disease has been found

Just as there are several types of pneumococci so now it appears that there are different types of the diplo streptococcus and evidence is accumulating to show that there is a considerable tendency to pleomorphism and perhaps mutation (Zozova unpublished data) As I have already said, the failure of a specific serum to help some patients might well have been due to the fact that in just these cases other organisms were found in the heart s blood at the time of death

A number of investigators have concluded that the diplo streptococcus cannot be the cause of the colitis because it can be found occasionally in the stools of apparently normal persons Actually this was to be expected, if only because pneumococci of a certain type are to be found in every human throat Incidentally it should be mentioned here that in a few cases of vague intestinal unrest in which the colon appeared to be normal but in which the stools contained the typical streptococcus the patients have returned after a year or so with definite colitis

One bit of evidence in favor of the view that the diplo streptococcus is at least the usual cause of the disease is to be found in the fact that before Logan and I began the use of vaccines made from this organism, we were able to do so little for patients with the disease that we felt rather hopeless about them As soon as we began to use the vaccine we were able to obtain what looked like a

type may extend to other organs o that infarction of the type seen in cases of endocarditis can eventually take place

The picture of a granular easily bleeding hyperemic and edematous mucous membrane together with narrowing of the lumen of the bowel cannot easily be confused with that of any other disease

Diagnosis

A well taken history is usually of great help in making the diagnosis of *chronic ulcerative colitis The symptoms usually begin insidiously with flatu* lence indigestion distress along the course of the colon and occasional loose stools Gradually there will be an increase in the frequency of the bowel move ments there may be some blood in them there w ll be some loss of weight and the appetite will fail Finally the patient will become pale and anemic he will be weak, thin and apathetic and his face will take on a worried look

The symptoms may persist unabated or there may be partial or complete remissions which last for weeks or months Remissions and exacerbations may continue in this way with each attack a little more severe and more distressing until the diarrhea is continuous and the patient becomes a chronic invalid, chained closely to a toilet room There will then be many bloody, mucopuru lent, rectal discharges containing varying amounts of feces The calls of nature will be urgent and there will be much tenesmus and straining at stool

In a few cases the early symptoms will be those of an acute fulminating illne s with a septic type of fever many bloody or purulent rectal discharges night sweats and herpes labialis In some respects this form of the disease is like pneumon a with the difference that the discharges are intestinal instead of bronchial and tracheal Severe cramps are often complained of The patient is *usually anemic and his face assumes a peculiar gray pallor In the severe* cases a peculiar body odor can be recognized There may be an anxious rather hopeless facial expression

Except for a diffusely tender abdomen there are no distinctive physical signs Digital examination of the rectum will immediately give a clue to the nature of the disease the lumen will be found to be narrowed and the wall will feel as if studded with soft nodular flat topped excrescences of mucous membrane.

Most helpful is the sigmoidoscopic examination In the early stages of the disease the mucous membrane will be slightly hyperemic with a finely granular appearance It will bleed easily In the later stages there will be miliary abscesses and shaggy ulcers separated by bands of granular looking and red dened mucous membrane

Very characteristic also is the roentgenologic picture obtained on giving a

Most of the mucous membrane is destroyed sometimes as much as 90 per cent of it and as a result, only hypertrophied islets of inflamed mucous membrane are left These may remain as bridges or tags or straps from which arise the pseudopolyps which can later become carcinomatous (Fig 2) The terminal

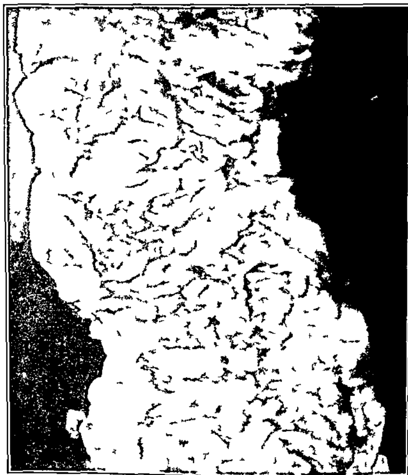


Fig 2 Large intestine from patient with chronic ulcerative colitis

portion of the ileum is involved only late in the course of the disease, and then numerous hard, enlarged, lymph nodes usually will be present in the mesentery

In most cases the disease begins in the rectum from whence it spreads to the cecum and finally to the terminal coils of ileum That the infection at times spreads into the blood is indicated by the not infrequent discovery at necropsy of multiple thrombi in the minute vessels of the intestinal wall, thrombi containing numerous masses of diplo-streptococci Thrombi and emboli of this

of the discharge will be seen to be made up of leukocytes and bacteria among which streptococci predominate

It is often helpful diagnostically to demonstrate the presence of the characteristic diplococcus The quickest and most satisfactory method of obtaining this organism is to make cultures from swabbings of the mucous membrane of the rectum or from the floor of one of the ulcers but sometimes it can be isolated by repeated culturing of the rectal discharges or stools The technic has been described in detail on page 219 of the book on Diseases of the Colon Rectum and Anus by Rankin Bargen and Buie[1] Briefly the cotton swab which has been rubbed on a rectal ulcer or dipped in a small quantity of feces or rectal discharge is used to inoculate several tall tubes of dextrose brain broth the medium introduced by Rosenow After six hours incubation material from the bottom of these tubes is transferred to new tubes of dextrose brain broth and into shake cultures of blood agar and incubated for twelve hours Often the organisms can be picked from this first blood agar plate but they are less likely to be overgrown in a plate made from the second tube of dextrose brain broth The typical colonies of the diplo-streptococcus can be recognized by the surrounding greenish zone in which there is slight hemolysis

The organism so isolated is lancet shaped and slightly larger than the pneumococcus it is gram positive and in early subcultures it appears in groups of only two or four It does not ferment inulin it usually does not ferment mannite and if it does the action is only slight It does ferment dextrose, lactose saccharose maltose raffinose and salicin On mannite agar it grows as a fine translucent colony It does not grow in plain agar except after repeated subculture and then only sparingly It does not grow on gelatin and it coagulates milk only slightly if at all After repeated subcultures it may tend to form chains like any other green producing streptococcus Injected into rabbits or dogs it can produce the typical lesions of ulcerative colitis as they are seen in man

Differential Diagnosis

Other forms of ulcerative enteritis must be thought of by the physician as he tries to make a differential diagnosis Foremost among these and most frequently confused with chronic ulcerative colitis is the ulceration caused by Endameba histolytica In this case the ulcers will probably be more circumscribed they will have raised margins with a zone of hyperemia just beyond and the crater will be covered by a fleck of mucus or necrotic debris Between the ulcers *the mucous membrane will be normal or fairly so There will be no* sign of that narrowing of the diameter of the rectum which is so characteristic of chronic ulcerative colitis When after finding this rectal picture the physi

barium enema (Fig 3) In the earlier cases there will be a loss of haustration and a narrowing of the lumen of the sigmoid flexure and descending colon In



Fig 3 Roentgenological picture after barium enema in patient with chronic ulcerative colitis

more advanced cases the whole colon will have smooth walls and will be considerably shortened

Examination of the rectal discharges with the unaided eye is of great value They consist usually of soft, semi liquid bloody muco-purulent masses composed mainly of pus but at times largely of blood This blood will be partly mixed with the stool and partly in the form of clots Microscopically, much

TABLE 2 — DISTRIBUTION OF 268 COMPLICATIONS WHICH OCCURRED IN 693 CASES OF CHRONIC ULCERATIVE COLITIS

Complication	*Cases*	*Per cent of 693*
Polyposis	69	10.0
Stricture of the bowel	59	8.5
Arthritis	30	4.32
Perirectal abscess	6	3.7
Perforation of the bowel	18	2.6
Cutaneous lesions	17	2.45
Malignant disease	15	2.16
Renal insufficiency	8	1.15
Splenomegaly	7	1.0
Endocarditis	7	1.0
Ocular disease	5	0.7
Rectal hemorrhage (fatal)	3	0.4
Renal calculi	2	0.2
Mesenteric thrombosis	1	0.15
Tetany	1	0.15

Treatment

The treatment of chronic ulcerative colitis now carried out by my colleagues and me is the result of years of experiment and study During the period from ten to fifteen years ago we together with most students of the disease felt rather hopeless about what could be accomplished medically Patients were given colonic irrigations containing various antiseptics They were given the usual antidiarrhœic drugs and perhaps some iodin by mouth They were put to bed and fed carefully but few showed signs of a real cure If they did improve and get back to work they soon fell ill again

Surgery — Under these circumstances it is not surprising that most clinicians were inclined to turn to the surgeon for help The hope was that a cure might be obtained either by deflecting the current of intestinal contents out of the abdomen as by an ileostomy or else by making a hole in appendix or cecum and, through this injecting disinfectant solutions The making of an ileosigmoidostomy was soon given up because it was found to be useless Obviously it can do little good to throw the ileal contents directly into that region of the bowel which is most injured by the disease Washing the colon through cecostomy or appendicostomy openings was also found to be unsatisfactory

Ileostomie continued to be made but the results obtained with them were rather discouraging In the first place as the operation used to be done it carried a tremendous risk because the patient was usually in poor shape and the

cian discovers typical amebæ or cysts in the stools the diagnosis will have been made

The ulcerations of tuberculous colitis are at times hard to differentiate from those of chronic ulcerative colitis A history of tuberculosis, the discovery of typical lesions elsewhere in the body, the fact that the disease is most marked in the cecum, and the finding of acid fast bacilli in the stools or sputum will help in making the diagnosis Tuberculous ulcers in the rectum can be recognized by their irregular shape their shaggy floors and their undermined edges They tend to coalesce into larger necrotic ulcers with patches of relatively normal mucous membrane in between

Cancer of the rectum not infrequently produces diarrhea with bloody rectal discharges and as a result, the patients are often treated for some time for colitis The slightest examination of the rectum with finger or proctoscope ordinarily should suffice to make the correct diagnosis Another disease that is occasionally confused with colitis is polyposis of the large intestine, and another is diverticulitis The latter rarely causes bleeding, but sometimes in the acute attacks there are small diarrheic movements with a little blood in them

In the acute fulminating cases of chronic ulcerative colitis the disease must be differentiated from bacillary or typhoid dysentery The bacteriologist s report will then be all essential in making the diagnosis A mild form of chronic ulcerative colitis must of course be thought of in every case of diarrhea in which a definite cause cannot be found

Complications and Sequelæ

As one would expect with an infectious disease so severe and so prolonged as is chronic ulcerative colitis there are many possible complications and sequelæ Table 2 lists 268 such complications which occurred in 693 cases of chronic ulcerative colitis observed by me and shows the frequency with which they are likely to appear In looking over this list the reader should remember that one patient commonly suffered with several complications Thus, in one instance, endocarditis, arthritis erythema nodosum iritis and perirectal abscesses overwhelmed the poor victim in another case perirectal abscess polyposis and cancer followed one after the other Some patients with ulcerative colitis recover without untoward incident while others suffer with one serious complication after another until death ends their sufferings As will be seen from the table, the most frequent sequela of the disease is polyposis This will be described at length in the section on rectal polyps

patients in whom the disease is not complicated by the presence of strictures fistulas, polyps or carcinomatosis have been relieved of their symptoms

A number of writers have been inclined to the view that the results which my colleagues and I have obtained with vaccine would have been the same if we had used any form of foreign protein Actually we and many others have tried non pecific vaccines and sera and have found them to be either useless or else of temporary value in only occasional cases They have little effect on the diarrhea but sometimes they have some on the arthritis which occasionally accompanies the colitis Antidysentery serum has given favorable results in a few cases but in others the serum sickness was so severe that the good effects were nullified

Removal of Foci of Infection — It is my belief that all demonstrable or accessible foci of infection should be removed if possible because they may serve as depots from which reinfection of the bowel can take place If one wishes to leave no stone unturned in the treatment of the disease one should remove teeth with periapical abscesses and suspicious looking or definitely infected tonsils Unfortunately because of the presence of a tender and inflamed rectal wall these patients cannot stand the massage which would be necessary to clear up prostatitis Usually when this focus is present it has to be left alone

Nursing Care — It is important to keep the patient warm and to maintain the level of the body fluids This level can easily be lowered when there are many watery movements As in all acute diseases and other forms of diarrhea rest in bed is highly desirable and often exceedingly helpful All patients with fever should be in bed until the temperature is normal and then they should get up slowly *Only moderate activity should be allowed until the patient is well* on the road to recovery Freedom from worry and emotional strain is important Fatigue and nervous excitability interfere with the patient s progress and they have been known to precipitate exacerbation of the disease Plenty of sleep is helpful

Diet — Many physicians undoubtedly restrict too greatly the amount of food allowed these patients and as a result they lose in strength and in their ability to fight the infection The ideal foods are those which are digested almost entirely in the small bowel and which thus leave very little residue for the colon Some of the foods with the least residues are beef rice white bread Italian pastes sugar well cooked and strained cereals cooked eggs butter and cream As already stated every effort should be made to give these patients a diet sufficiently rich in calories so that body weight can be maintained When the patient is up and about we try to give a diet that will supply approximately 3000 calories

Because these patients often must be careful of the diet for a long time the

wall of the bowel and the lymph channels in the mesentery were almost always heavily infected. To be sure, when the patient did survive, he generally gained much weight and improved in health, but sooner or later he was back clamoring for an operation that would close the stoma. When this was done, the condition in the colon generally flared up again, and the patient was soon back where he or she was before.

During recent years since the introduction of vaccines and a specific serum, we at the Mayo Clinic have resorted to ileostomy in only a small fraction of the cases. Actually in the years from 1921 to 1931 inclusive 1333 new patients with chronic ulcerative colitis were treated, and during this time only 92 ileostomies were made. That the results still are bad can be seen from the fact that [illegible]7 of the patients died in the hospital, and we know of 12 more who have since passed away.

Disinfecting Irrigations. — My experience and that of many other clinicians is that the amount of good accomplished by the so-called disinfecting irrigations is offset by the amount of irritation that they produce. Because of this irritation my colleagues and I have, for many years, relied only on cleansing enemas of warm physiologic saline solution and have given even these to only a few patients. Occasionally when the bowel is washed out at bedtime, the diarrhea stops long enough so that the patient can get to sleep. The essential point to be remembered is that no matter how powerful a disinfectant is used, one cannot hope, by injecting it as an enema, to eradicate the infection present. The trouble is that the disease extends too deeply through all the layers of the bowel; it is out in the muscle, it is in the mesentery and sometimes it is even in the blood stream. Obviously the only way in which such an infection can be reached is through the blood. One must raise the general body resistance just as is done in cases of tuberculosis, and one must use a specific antiserum.

Vaccines and Serum. — Today at the Mayo Clinic the treatment of ulcerative colitis consists of, first, attempts at immunization with vaccine and serum made from the organism found in the diseased tissues; second, the removal of all foci of infection; and third, the giving of a low residue, high caloric diet.

The vaccine should be used in the milder and earlier cases. Obviously it can be of little value when the patient is overwhelmed with infection and is running a high fever. The only thing that can help then is an antiserum, and now that it is available it is often of tremendous value. (It can be secured from Mulford and Parke Davis Co.) In some cases its administration is followed by a striking fall in the patient's temperature and a disappearance of the pronounced intoxication. We have used it now in more than 700 cases and although at times it fails us, the results obtained surpass those secured with all other forms of treatment. In recent years approximately 75 per cent of our

Days 13 and 14 cream added to milk so that each of the 2 or 3 glasses taken contains half milk and half cream bland fruit canned or cooked peaches apricots pears strained apple sauce baked apple without skin 1 serving

Days 15 and 16 Tomato juice ½ glass or tomato jelly

Days 17 and 18 Whole cooked vegetable 2 servings (vegetable puree added on days 7 and 8 omitted) including as desired young tender carrots beets spinach squash peas string beans asparagus tips potato any way except fried

Days 19 and 20 Shredded green lettuce cut very fine Plain mayonnaise or cooked dressing may be used on the lettuce

These in addition to the foundation diet will constitute a full diet containing 80 gm of protein and 3000 calories Jelly or jam without seeds may be served if desired Beverages should not be iced The patient is instructed to eat ice cream slowly Condiments such as mustard horse radish catsup vinegar and highly seasoned sauces or relishes are best avoided To avoid the stimulus to peristalsis food is not given between meals

Contrary to the usual assumption milk is not a low residue food, and it is not well tolerated by many of the patients It should therefore be used only with caution and in small amounts Boiling the milk seems to make it only slightly more digestible A number of writers and particularly Larrimore have been of the opinion that the good results sometimes seen when these patients are given enough food is due to the high vitamin content of the diet

It can easily be seen that the amount and quality of the food given to these patients must depend largely on the severity of the disease When the symptoms are acute the patient may be able to take only a small amount of highly concentrated food In the worst cases it may be necessary for a time to give nothing but liquids by mouth A solution of glucose can be injected intravenously and large amounts of physiologic saline solution can be injected under the skin

Camphorated tincture of opium and codein often are helpful in cases in which there is much pain and tenesmus or in which the stools are being evacuated so frequently that the patient is becoming exhausted At times the insoluble powders such as bismuth tribasic calcium phosphate and kaolin are helpful The first two can be given in doses of from 4 to 8 grams (1 to 2 drams) 3 or 4 times in the 24 hours Kaolin can be given in doses of 30 to 60 gm (1 or 2 ounces) Occasionally hot stupes seem to give the patient comfort

Drugs — No single drug has been found that will help more than an occasional patient Among the substances used may be mentioned iodine gentian violet and arsenic Freshly made tincture of iodine is given on a full stomach in doses of from 5 to 15 drops in a glass of water 3 times a day for 1 week out of the month If no improvement is noted in the first week its administration should be stopped Gentian violet can be prescribed in 0 03 gm (½ grain) tablets from 3 to 5 of these being taken every 24 hours Enough should be

physician must see to it that the food eaten contains all the necessary vitamins and chemical elements Vitamins can be supplied in concentrated form, in fruit juices in yeast, butter wheat germ, cod liver oil extract, or irradiated ergosterol *A sample bland diet for the patients with chronic ulcerative colitis is* given in the following table

Dietary Regimen for Patients with Chronic Ulcerative Colitis

Foundation diet given on days 1 and 2[1]

Breakfast	*Dinner*	*Supper*
Cereal bland 1 serving with cream ½ cup and sugar	Meat soup without vegetables 1 serving	Steamed rice 1 serving[4]
Bacon 2 strips	Meat 1 serving (liver three times a week)	Meat or fish 1 serving or 2 eggs
Egg 1	*Potato 1 medium sized any* way except fried	Bread white or rye 1 slice or *equivalent amount of* biscuit zweibach cracker and so forth
Toast 1 slice	Gravy if desired	Butter 2 squares
Butter 2 squares	Bread white or rye 1 slice or an equivalent amount of biscuit *zweibach* cracker and so forth	Bland dessert[5] no fruit 1 serving
Coffee if desired	Butter 2 squares	*Cream 2 tablespoonfuls*
Brewers yeast[3]	Bland dessert[5] no fruit, 1 serving	Tea if desired
	Cream 2 tablespoonfuls	Sugar
	Tea if desired	Brewers yeast
	Sugar	
	Brewers yeast	

[1] Given on admission contains approximately 60 gm of protein and 2000 calories

[2] Cream of wheat farina *puffed rice puffed wheat corn flakes rice krispies and strained* oatmeal

[3] Brewers yeast 200 mg standardized vitamin fraction is given with each meal

[4] Potatoes or other substitutes for rice are allowed if the patient is doing well

[5] Custards cornstarch puddings junkets gelatin desserts without nuts or fruit, plain rice puddings simple cakes and cookies cooked fruit whips and plain ice cream

The following foods may be added to the foundation diet as rapidly as the patient s condition permits

Order of Additions

Days 3 and 4 one banana very ripe and cod liver oil 1 to 3 teaspoonfuls daily
Days 5 and 6 orange juice ¼ glass
Days 7 and 8 vegetable purée 2 table poonfuls
Days 9 and 10 milk in the form of cream soup or milk toast
Days 11 and 12 whole milk 2 glasses

serum Unfortunately a recurrence still can take place years after an apparent cure The patient therefore should be watchful of his health and should try to avoid chilling of the body over exertion and fatigue Colds and infection of all kinds are dangerous

Most of those persons who receive adequate treatment early in the course of the disease can be cured The mucous membrane of the colon regenerates and in approximately 40 per cent of the patients in whom the first roentgenogram made showed a smoothing of the outline of the colon there will later be found some return of the normal haustration

Unfortunately even after the mucosa has returned practically to normal and the patient is well there is still the small possibility that some day he will succumb to a fulminating type of general carcinomatosis of the colon This peculiar complication will be described in the section on polyposis

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J A B

Intestinal Tuberculosis

History —According to Brown and Sampson Kline and others it is convenient to divide the history of our knowledge in regard to intestinal tuberculosis into four periods

1 From the time of Hippocrates to that of Bayle (1816) During this long epoch it was known that diarrhea frequently occurred late in the course of pulmonary tuberculosis but little thought was given to the possibility that the loose stools might be due to lesions in the bowel similar to those in the lung Sydenham pointed out years ago that in cases of phthisis the appearance of diarrhea meant that the end was in sight

2 From the time of Bayle to that of Louis and Rokitansky During this period the lesions of the intestine were described and recognized as being tuberculous

given to color the stools blue This drug can be taken for some time, and occasionally it seems to produce improvement Arsenic is a dangerous drug and should be employed only as a last resort because it may cause a flare up in the disease Once this happens it is very hard to do anything for the patient

Those physicians who use irrigations have employed many of the so-called intestinal antiseptics The favored ones are acriflavine hydrochloride, in a 1 to 4 000 solution mercurochrome 220 soluble", in a 1 or 2 per cent solution, silver nitrate 0 06 to 0 12 gm (1 to 2 grains) in a liter (quart) of water and copper sulphate, 0 12 to 0 24 gm (2 to 4 grains) in a liter (quart) of water Preparations of silver such as argyrol, are somewhat dangerous as the continued use can produce argyria As I have said before warm physiologic saline solution is the least irritating and the most useful of all the solutions that I have tried

Some physicians have advised blowing into the rectum powders such as calomel and bismuth but these drugs could be of value if at all, only in those early cases in which the lesions are located in the last few inches of the bowel

Transfusions of blood often are of great value particularly in those cases in which the patient has bled profusely from the bowel and has become markedly anemic and weak In such cases repeated transfusions may do more than anything else to restore the patient to health Transfusion is particularly efficacious in cases of children afflicted with the disease Often it is well to give from 150 to 200 c c of blood once a week

Surgery in Complications — After everything possible has been done in a medical way for these patients the surgeon may still have to be called in Today at the Mayo Clinic an ileostomy is made only in the presence of complications such as stricture polyps perirectal abscess, fistula, or possibly carcinoma of the colon The operation can be done with somewhat lessened risk if the patient is in good condition and the colitis is under control The so-called one barrel ileostomy of Rankin is the operation of choice The development of complications such as rectal abscesses and colonic perforations will make operation obligatory but the work should then be done as quickly as possible and with the least trauma Occasionally after the disease is well healed, the formation of strictures may make a colectomy necessary

Prognosis

Some of the patients who are relieved of their symptoms by medical treatment, will relapse, but in such cases the beginning symptoms are usually mild and they can be brought under control quickly again by the use of vaccine or

accounted for in the following ways If as seems most probable the infecting organisms enter by way of the intestinal mucosa the lesions ought to be most abundant in that part of the bowel in which the digestive residues slow down in their progress and stagnate without at the same time becoming solid and dry As every one know these conditions are to be found only in the ileocecal segment of the intestine and it is here that Nature has concentrated many masses of lymphoid tissue to aid in the fight against infection

Apparently when the invaders are too numerous some of the nodes in the mucous membrane are overwhelmed they become *necrotic and in breaking* down they give rise to ulcers Probably before this happens the bacteria follow along the lymphatic vessels to the root of the mesentery where they produce necrosis and *calcification of the nodes*

One can see in the wall of the bowel all stages in the evolution of the tuberculous process from the formation of tubercles to caseation, ulceration and scar formation The ulcers may begin as mere *abrasions which grow and coalesce* with others to form large holes in the mucosa Typical ulcers are as oriated with marked infiltration of the surrounding tissues the edges are everted and there is considerable undermining The floor of the ulcer may be formed by the submucosa or muscularis mucosa and it is often covered with necrotic debris On the serous surface opposite the ulcers one may find groups of tubercles In the small intestine the ulcers are irregular in shape and distribution in the colon they usually run transversely to the long axis and in both places they tend to girdle the bowel like a chain of sausages

In Goldberg Sweany and Brown s series of 230 cases coming to post mortem examination there was only one in which the ulceration was limited to the colon and only twelve in which the lesions were in the cecum and colon alone

Hyperplastic Tuberculosis —There is another type of intestinal tuberculosis which is sometimes found in the ileocecal region and which in a small percentage of cases seems to be primary in the bowel at any rate it may occur in persons whose lungs have never given trouble This is the tuberculoma of Brown Peraire and Dowdle or the neoplastic tuberculosis of the French authors Ferrando and Saloz reported it as a primary lesion in 2 3 per cent of 2,058 post mortem examinations of tuberculous patients

In these cases there is a tumor like thickening of the wall of the bowel which is produced by proliferation of connective tissue This extends through all the layers of the bowel wall and converts it into a thick walled tube with a narrow lumen Such thickenings of the bowel occasionally will be found nearer the stomach and rarely there will be several in different segments of the gut Apparently the type of tubercle bacillus which produces these leisons does not cause caseation

3 From the time of Louis and Rokitansky onward, when the lesions were carefully studied and their severity and extent correlated with the seriousness of the patient's symptoms Some attempt was made also to link gastrointestinal symptoms with tuberculous toxins and with reflexes originating in the lungs

4 From the development of a roentgenologic technic for intestinal examination to date This technic showed abnormalities in intestinal motility and defects in the outline of the walls of the gut Particularly helpful was the early work of Stierlin

Incidence

Adults seem to be more susceptible to intestinal tuberculosis than are children In one group of tuberculous children Bollinger found from 30 to 40 per cent with intestinal lesions and in another group of 1,346, Biedert found involvement of the bowel in 5 per cent On the other hand, in a group of 230 adults dead of tuberculosis intestinal lesions were present in 80 per cent The comparatively rare primary tuberculosis of the intestine is more commonly found in children but this may be due to the fact that they often drink milk which contains tubercle bacilli

Pathology

There is no uniformity of opinion concerning the mechanism of the development of tuberculous enterocolitis Archibald thinks the hematogenous route is the most probable that is that the breaking down of a peribronchial or mesenteric lymph node leads to a scattering of the bacteria by the blood stream Goldberg Sweany and Brown have stressed the possibility of a dispersion through the lymphatic channels but the route through bronchi esophagus and stomach now appears to be the most important one (Goldberg and Smithies)

Rokitansky's description of tuberculous enterocolitis in his "Manual of Pathologic Anatomy" published in 1849 still can be read with profit Most students of the disease classify the lesions under three headings (1) hypertrophic or hyperplastic (2) sclerotic or fibrous and (3) ulcerative The last named is by far the most common

The lesions are usually found in the terminal portion of the ileum and in the cecum Brown and Sampson found this region involved in 85 per cent of the cases Any part of the digestive tract may be affected but the frequency of involvement varies inversely as the distance from the ileocecal sphincter As Goldberg, Sweany and Brown point out this distribution of the lesions can be

accounted for in the following ways If as seems most probable the infecting organisms enter by way of the intestinal mucosa the lesions ought to be most abundant in that part *of the bowel in which the digestive residues slow down in* their progress and stagnate, without at the same time becoming solid and dry As every one knows, these conditions are to be found only in the ileocecal segment of the intestine and it is here that Nature has concentrated many masses of lymphoid tissue to aid in the fight against infection

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Diagnosis

In the common form of tuberculosis of the bowel the most important item in the diagnosis is the fact that the patient has or has had fairly extensive tuberculosis of the lungs or some other part of the body As has already been pointed out such disease in other organs is present in from 95 to 97 per cent of the cases Babinsky was unable to find pulmonary lesions in only five of 285 persons who came to necropsy with intestinal tuberculosis

In the presence of active pulmonary tuberculosis, the finding of acid fast bacilli in the stools is of little diagnostic value because this discovery can be made in from 85 to 95 per cent of all patients who are swallowing tubercle bacilli in the sputum

When a person is known to have pulmonary tuberculosis, the symptoms which suggest the presence of intestinal involvement are commonly nervousness dizziness irritability, failing appetite, abdominal discomfort, flatulence and possibly constipation Almost any type of digestive disturbance may be complained of and in addition the patient will probably fail to improve in spite of the fact that the pulmonary lesions seem to be healing

As the disease in the bowel progresses there will probably be some complaint of discomfort pain and diarrhea perhaps alternating with constipation The appetite will be completely lost there may be nausea, and because of the inability to eat the patient will lose weight

It has been said that diarrhea in cases of tuberculosis means involvement of the colon and constipation involvement of the small intestine This is not always true When the lesions in the small bowel are extensive, diarrhea usually is present but in moderately advanced cases there may be intervals during which the patient is constipated During attacks of diarrhea the stools usually are profuse thin watery and perhaps foul smelling, at times they are viscous Blood usually can be detected with chemical tests, but only rarely can it be seen with the naked eye

In the hypertrophic type of intestinal tuberculosis, symptoms of obstruction may be the first ones noted or the patient may discover a tumor in the right lower quadrant of the abdomen Sometimes the main symptom is lack of energy At intervals there will be attacks of constipation with much gurgling and rumbling in the bowel colicky pains and possibly nausea and other symptoms of back pressure Not infrequently the patient is operated on for subacute appendicitis

On physical examination in patients with a common form of intestinal tuberculosis the abdomen may feel doughy a mass may be felt, or the colon may feel like a cord No single clinical laboratory test for intestinal tuberculosis is entirely trustworthy When lesions are so extensive that they can be

seen through the proctoscope signs of tuberculosis in other organs usually will be abundant Tuberculous ulcers in the rectum show undermined indurated and reddened margins and an irregular elevated gray base Small yellow tubercles may perhaps be seen scattered over the floor of the ulcers These ulcers do not bleed easily

According to Carman a positive and independent roentgen diagnosis of tuberculous colitis is difficult to make as there are no pathognomonic signs the filling defect and the absence of the normal barium shadow in the cecum are signs of an ulcerative lesion Tuberculosis however has such a predilection for the ileocecal region that any abnormality seen in this part of the intestine especially if associated with pulmonary tuberculosis probably is of tuberculous origin

With the roentgenoscope one can see filling defects spastic contractions and signs of obstruction The filling defects are due to the ravages of the disease plus spasm Under pressure of the enema the cecum and ascending colon will be seen to fill irregularly and the diameter of this part of the bowel probably will be narrowed The normal haustral markings often will be absent When the pressure of the enema is relieved by clamping the tube the involved region in the bowel usually empties and remains empty while the normal segments stay filled Carman reported seeing similar signs occasionally in ulcerating carcinoma of the cecum and in chronic ulcerative colitis

Brown and Sampson have emphasized the importance of hypermotility of the bowel as a sign of tuberculous colitis Stierlin in 1911 first noticed that the column of barium coming down the digestive tract seemed to skip the cecum and ascending colon This emptiness of the inflamed region of the bowel is probably due to its greater irritability and responsiveness to the presence of material in the lumen The usually sluggish ileum may through inflammation, become just as irritable as the jejunum and as insistent on keeping itself empty

According to Brown and Sampson the presence of spasm or of spastic filling defects an irregular contour of the bowel lack of haustration failure of the cecum or other parts of the proximal colon to retain barium dilatation of and stasis in one or more coils of the small bowel ileac stasis and gastric retention all suggest the presence of intestinal tuberculosis

Complications

Brown and Sampson have listed the complications and sequelae of intestinal tuberculosis as follows (1) secondary infection (2) hemorrhage (3) stricture (4) localized tuberculous peritonitis causing adhesions effusions abscesses and fistulas (5) generalized tuberculous peritonitis (6) perforation of the bowel (7) general miliary tuberculosis (8) amyloid disease (9) intussusception and

(10) carcinoma. To these might be added (11) fistula in ano, although this is much less common than was formerly supposed and (12) polyposis.

Other workers have reported a number of unusual complications. Eichoff saw a case of ileovesical fistula and Vater saw a patient with stenosis of the ileocecal sphincter which led to obstruction of the bowel by a mass of water melon seeds. Levinson reported a case of fatal hemorrhage into the spleen from a tuberculous ulcer of the bowel. Wiechers saw a marked generalized edema comparable perhaps to a "war edema." Holden saw acute intestinal obstruction due to a healed patch of tuberculous enteritis. Hartman noted the association of cecal tuberculosis with epithelioma, and Cain and Monnerot Dumaine saw a case of perforation of the sigmoid flexure. Bruning recorded a case in which the first symptoms of intestinal tuberculosis were those of acute obstruction, and Cloganer described cases in which tuberculous colitis was confused with acute appendicitis. Masson and McIndoe, Counseller, Rogue, Patel and Morenas have reported cases of obstructive tuberculosis of the small bowel.

In general it may be said that the major complications of intestinal tuberculosis are not unlike those of other ulcerative and obstructive intestinal lesions.

Treatment

There is no specific treatment yet available for the common type of intestinal tuberculosis which is secondary to disease of the lungs. The physician must go on treating the patient very much as he or she was treated before, with rest in bed and heliotherapy. As soon as the presence of intestinal lesions is suspected, the object of treatment must be to take some of the burden off the inflamed and handicapped bowel. To do this the physician will want to prescribe a smooth, rather low residue diet; he will probably want to let up on the forcing of food, and he will be particularly careful to stop the giving of milk because this leaves a large residue to be handled by the lower ileum where most of the lesions are situated.

In a number of large tuberculosis sanitoria the smooth diet is used routinely for all patients who are seriously ill and in whom the chances are that intestinal lesions are either present or will soon appear. In such a diet, roughage is eliminated so far as possible and fresh fruit juices and purees are used instead of the more fibrous raw fruits, vegetables and salads. If with the small amount of fecal residue the bowels do not move sufficiently well, the colon may be washed out with enemas of physiologic saline solution. A number of writers have stressed the importance of giving a diet rich in vitamines, but they have given no proof of the special efficacy of this measure.

In some sanatoria colonic irrigations are given especially if the diarrhea is severe Obviously irrigations can be of little value when the lesions are situated almost entirely in the lower part of the ileum Enemas of warm physiologic saline solution may however be helpful especially when given about bedtime so that the patient can get more rest and sleep

Davis and others have emphasized the importance of heliotherapy Erickson has reported marked improvement in cases treated with ultra violet light and Talbot claims that the effects of ultra violet light are superior to those of sunlight The German workers and particularly Kellner and Reh have reported good results from roentgeno-therapy

A large group of workers including Jelks Laney and Checten have expressed the belief that it is worth while to treat intestinal tuberculosis with injections of oxygen into the peritoneal cavity

Many drugs have been used among which may be mentioned calcium arsenic and mercury Bernard Salomon and Thomas reported favorably on the use of stovarsol and treparsol Curti has had some success with the use of calcium and parathormone and Ringer and Minor and Roberts have reported favorable results following the long continued use of calcium chloride injected intravenously For active diarrhea Brown and Sampson have suggested the use of drop doses of creosote in a capsule with 0 016 gm ($\frac{1}{4}$ grain) of iodoform after meals Fifteen milligrams ($2\frac{1}{2}$ grain) each of phenyl salicylate and Tully powder (pulvis morphinæ compound consisting of morphine sulphate 0 5 gm camphor 0 5 gm precipitated chalk 10 gm and glycyrrhiza 10 gm) may be given every four hours in severe cases Our experience at The Mayo Clinic makes us doubt if any of these drugs has much value

A number of writers have advocated operation on patients with ulcerative tuberculosis of the bowel but leading authorities agree that this is inadvisable except in the occasional cases in which the symptoms arising in the bowel are more threatening and more serious than those arising in the lung In a recent article Brown and Sampson express great pessimism in regard to the effects of operations for the relief of the common type of secondary intestinal tuberculosis

The problem is different in the case of the hyperplastic stenosing type of tuberculosis which is found usually in patients who are not suffering from active pulmonary tuberculosis In these cases the main symptom often is that of obstruction and this must be relieved promptly by operation Occasionally when the patient is in good condition the affected loop or loops of bowel can be resected but often as when the patient is run down and in poor condition it is safer to short-circuit first and then wait until the patient has regained his health If a mouldering pulmonary lesion is present this will then have an opportunity to heal and later the risk of removing the diseased segment of bowel will not be great It is possible that in some cases the affected segment might even be

allowed to remain because with the cessation of function of the bowel, the lesions tend to dry up and heal

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J A B
W C A

Tumors of the Small Bowel

Benign and malignant tumors of the small intestine are uncommon in comparison with lesions of the stomach and colon At the Mayo Clinic only one per cent of the carcinomas of the gastro-intestinal tract occur in the small bowel They may originate at any point in duodenum, jejunum or ileum Lymphosarcoma likewise is a rare lesion, although according to Boyd, it is seen more frequently in the small than in the large bowel

The benign tumors of the small bowel, in the usual order of frequency of occurrence are adenoma myoma lipoma lymphangioma and hemangioma They usually fail to give rise to symptoms until they are large enough to obstruct the lumen of the bowel Then they produce colicky pain with bloating and borborygmus Not infrequently the bowel grips the tumor and tries to force it onward and as a result an intussusception is formed Comfort found that this accident occurred in five out of twenty three cases of lipoma of the small bowel

Rarely the surface of the tumor will become ulcerated and will bleed, or changes in the blood supply will result in congestion edema and ulceration Any one of these accidents is likely to produce symptoms that will indicate the presence of something seriously wrong but just what it is may not be discernible until the abdomen is opened The discovery of occult blood in the stools will suggest that the lesion is within the lumen of the digestive tract

The signs and symptoms of the malignant tumors of the small bowel are largely those of obstruction, to which is often added anemia due to the oozing of blood In rare instances large hemorrhages may take place but usually the blood is present in the stool in only small amounts With both the benign and the malignant tumors the examiner will occasionally be able to feel a small mass which slips away from his hand and gets lost so often that he cannot be sure about it

Roentgenographic signs of a neoplasm in the small bowel are the same as in any other portion of the gastro-intestinal canal namely there is a filling defect which encroaches on the lumen of the bowel and is associated with a mass that can be palpated Unfortunately the barium meal goes through the small bowel so rapidly and outlines it so poorly that it is not easy for the roentgenologist to find a lesion there even when he is looking carefully for it

A 'scout film' of the abdomen made before the giving of an opaque meal will sometimes be of great value especially when it shows a dilated loop of bowel filled with gas and marked with the typical lattice or accordion pleating cross-striations due to the presence of the Kerkringian folds This always means obstruction of the small bowel In addition there may be the typical roentgenologic picture of loops partly filled with fluid which is limited above by a straight line

The only treatment for tumors of the small bowel is surgical removal In the presence of multiple lesions or obstructing metastases a palliative short circuiting operation may be the only procedure possible Occasionally not even this is possible

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P W B

The Digestive Disturbances Associated with Constitutional Inadequacy

One of the commonest and most important diseases seen every day by the gastro-enterologist is constitutional inadequacy It is probably best to avoid the term constitutional inferiority because this may offend or humiliate or antagonize the patient besides many of these people are far from inferior in their intellectual attainments One has only to read the Life and Letters of Charles Darwin to get the picture of an extremely able man whose nervous system was entirely inadequate to stand the strain and stress of even a quiet

and sheltered life When he talked to a friend in the evening he was likely to get so tired and excited that he did not sleep that night, and as a result he vomited all the next day In many cases nervous system and body and glands of internal secretion all seem to be inadequate together, but occasionally one sees a decidedly frail nervous system in a big well nourished body

The trouble seems in most cases to be hereditary in origin Often several relatives will be small and thin and unable to stand the strain of life, and some times if one searches carefully one can find psychopathic or definitely insane ancestors or siblings I feel sure that in many cases the defect is inherited as a variant or an equivalent of the one that produces insanity, perhaps there are not enough defective genes to produce an unbalanced brain but there are enough to produce a nervous system that cannot "stand the gaff of life Sometimes the defect is brought out by hardship unhappiness and strain, but these added causes are not necessary as is shown by the fact that the disease often attacks the carefree children of the rich

It is highly desirable that more physicians throughout the world learn to recognize this type of patient in time to save him or her from having to undergo all sorts of time-consuming nerve racking and expensive diagnostic and thera peutic measures With the best of intentions many of us in the medical pro fession are now giving these poor constitutional inadequates a 'raw deal", and it is time that we learned to handle them more understandingly, helpfully and sympathetically I can remember a man who in the course of nine years was sent to the hospital ten times for abdominal operations which did not help him I doubt if any one of these operations would have been performed if the surgeon had ever taken the time to sit down and analyze the man s long ram bling tale of woe Like most of these patients he came in with a story of abdominal pain but a little cross questioning soon revealed the fact that his trouble was really not a pain but a vague flatulent uneasiness and burning Later there came the admission that this distress in the abdomen had always been a minor matter The real troubles were the feelings of weakness and fatigue, the tensions in the head the migrainous headaches the spells of de pression and of horrible but indescribable mental distress and worst of all the feeling that his job of sorting mail in the post office was too strenuous and too full of responsibility for him It was more than he could bear, and for years he wanted to flee from it and from the hurly burly of the city, he felt that if only he could get a little chicken ranch in some lonely place he would be well, but a large family chained him to the one little source of income that he had

The younger and more scientifically trained physicians today need to learn first the importance of getting the whole story from the patient and second the hopelessness of trying to make over permanently a constitutionally inade quate person by removing teeth tonsils appendix gallbladder or anything else

even when definite disease has been found in or about these organs The physician must give up not only the idea of curing these people but also the hope that if he will only search hard and long enough he will find somewhere in the body one lesion or disease that will explain the whole clinical picture In most cases he could not find such a lesion even if the patient were to die suddenly and be subjected to careful post mortem study

Just as the physician must give up the idea of working a spectacular cure so also the patient must acquiesce if possible he must be made to understand his problem he must learn to live as best he can with his handicaps and he must bring to a close his ever hopeful pilgrimage from the physician to the clinic to the quack and back again to the physician There are times of course when there are definite indications for operating on a patient who shows a marked constitutional inadequacy but then the work should be done only with reluctance and only when it seems that some definite or dangerous handicap can and should be removed The patient can be promised relief from a local distress but he must not be told that he is going to be cured and restored to perfect health

W C A

Digestive Disturbances Associated with Migraine

The gastro-enterologist sees so many patients with migraine that he must learn to recognize the disease in all its disguises Unless he learns to do this early in his career he is likely to recommend useless operations to a number of these poor sufferers

Most patients with migraine go to the gastro-enterologist because they cling to the hope that if he would only cure their constipation and relieve their symptoms of indigestion they would be well Actually in most cases they must be sent away disappointed There is no doubt that occasionally constipation will serve as one of the sources of irritation that bring on an attack of migraine but it isn t an essential cause as is shown by the fact that there are innumerable persons with severe migraine whose bowels move perfectly There is no doubt also that in some cases migraine can be brought on by the eating of certain foods but unfortunately the number of such patients appears to be small

The first essential in the study of these patients is a carefully taken history If, as usually happens it is found that the patient never has any indigestion except when he has a headache and if the headache always comes first the physician may be almost certain that he is dealing with a disease of the brain or its blood vessels and that it is useless to open the abdomen It is useless to remove appendix or gall bladder because the disease is not there the digestive

and sheltered life When he talked to a friend in the evening he was likely to get so tired and excited that he did not sleep that night, and as a result he vomited all the next day In many cases nervous system and body and glands of internal secretion all seem to be inadequate together, but occasionally one sees a decidedly frail nervous system in a big well nourished body

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It is highly desirable that more physicians throughout the world learn to recognize this type of patient in time to save him or her from having to undergo all sorts of time consuming nerve racking and expensive diagnostic and therapeutic measures With the best of intentions many of us in the medical profession are now giving these poor constitutional inadequates a 'raw deal', and it is time that we learned to handle them more understandingly, helpfully and sympathetically I can remember a man who in the course of nine years was sent to the hospital ten times for abdominal operations which did not help him I doubt if any one of these operations would have been performed if the surgeon had ever taken the time to sit down and analyze the man s long rambling tale of woe Like most of these patients he came in with a story of abdominal pain but a little cross questioning soon revealed the fact that his trouble was really not a pain but a vague flatulent uneasiness and burning Later there came the admission that this distress in the abdomen had always been a minor matter The real troubles were the feelings of weakness and fatigue, the tensions in the head the migrainous headaches, the spells of depression and of horrible but indescribable mental distress, and worst of all, the feeling that his job of sorting mail in the post office was too strenuous and too full of responsibility for him It was more than he could bear and for years he wanted to flee from it and from the hurly burly of the city, he felt that if only he could get a little chicken ranch in some lonely place he would be well, but a large family chained him to the one little source of income that he had

The younger and more scientifically trained physicians today need to learn first, the importance of getting the whole story from the patient, and, second the hopelessness of trying to make over permanently a constitutionally inadequate person by removing teeth, tonsils, appendix gallbladder or anything else

The Digestive Disturbances Associated with Arteriosclerosis, Hypertension, Heart Failure and Cerebral Thrombosis

The gastro-enterologist is not infrequently asked to see an elderly man or woman who is complaining of gas pressing up under the heart belching loss of appetite vague indigestion and abdominal distress loss of weight and strength, and perhaps loss of interest in life and the ability to work Not infrequently the clinical picture strongly suggests the presence of a hidden carcinoma and the patient has to be studied with the greatest care Roentgen ray examinations must be made of stomach and colon, the stools must be studied for occult blood, and the physician must examine as best he can every part of the body in which carcinomas tend to grow

Often however the experienced clinician will get the right hunch or will make the correct diagnosis as soon as he takes the history He will bring out many highly significant details which curiously enough the patient did not think were worth talking about In some cases the physician will dig out a story of one or more mild attacks of anginal pain following over-exertion or excitement He may find that the symptoms were always worse after the patient had dug in his garden or had played too many holes of golf The electrocardiogram may show signs of injury to the heart muscle and the symptoms will improve most when the patient is made to rest Not infrequently a high blood pressure will be found, and it will be obvious that the heart is failing under the burden In many of these cases belching seems to be practiced voluntarily in an effort to relieve substernal distress arising in the heart When flatulence is severe it seems probable that changes in the composition of the blood gases due to the embarrassment of the circulation bring about a failure of some kind in the mechanism which normally causes intestinal gases to be carried away by the blood stream and excreted by the lungs

In other cases careful questioning will elicit a clear story of one or more slight cerebral accidents The acute indigestion which apparently started the whole trouble came suddenly Perhaps on waking in the morning the patient found himself so dizzy that for several hours he was unable to take a step Associated with this there was sudden nausea and vomiting Afterwards there may have been some drowsiness for a day or two or there may have been some confusion in regard to the use of words or some uncertainty about the use of a hand or foot or a good deal of choking and coughing due to the entrance of food into the larynx

If one asks the patient about his memory, he will complain bitterly about the failure in it and if one asks the relatives about changes in character they will generally have much to say about the folly of the patient in being so depressed and apprehensive over nothing about his perverseness in refusing to

upsets seem to be due to some sort of a storm that comes down the vagus nerves Only when the patient tells a story strongly suggestive of the presence of chronic appendicitis or of cholecystitis with digestive upsets at times when there is no headache can one hope to accomplish something by operating But even when gall stones are found and removed, the surgeon must not promise relief from the migraine because this is a disease by itself, it is not caused by the cholecystitis but only made worse by its presence

The most puzzling cases particularly for the physician who has not had much experience with migraine are those in which the headache is not definite and is replaced to a large extent by severe pain in the upper part of the abdomen There are other cases in which the headache is mild, and the patient complains most of a terrible feeling of intoxication and depression Because this mental suffering is associated with nausea abdominal distress and perhaps epigastric pain and constipation the patient insists that the disease is all in the abdomen, and sometimes he succeeds in having himself operated on several times

The wise physician will make the correct diagnosis when he notices that the trouble comes in attacks somewhat resembling those of migraine, with periods of perfect relief in between He will bring out the fact that the attack begins perhaps with some aura or presentiment and that this is followed by the horrible feelings of depression and finally by the pain or nausea Often the patient will be found to come of a highly migrainous family, or rarely he will have an epileptic relative Physicians are probably correct in speaking of these disturbances as equivalents of migraine or epilepsy

Treatment

The treatment must be much like that used in cases of typical migraine If the patient has any warning of the attack the night before, a dose of luminal may be taken An effort should be made to avoid every possible excitant such as harmful articles of diet extreme fatigue eyestrain or loss of temper As soon as the attack appears some strong nerve sedative or antineuralgic drug should be taken Occasionally a dose of castor oil or some saline laxative will serve to abort the attack It will help if the patient will give in quickly and go to bed Whatever is done must be done quickly, because the longer the attack lasts, the harder it is to control Furthermore once the nausea has arrived, medicines given by mouth are useless because they are not absorbed

W C A

usually dull and located either in the epigastrium or else all over the abdomen Some patients described it as a heaviness or a feeling as if the bowels were distended with gas This type of distress usually disappeared within a few days after treatment was started

Severe abdominal pain was rare and when complained of it suggested the presence of gallbladder disease Constipation was troublesome in about one half of the patients, in 23 per cent the bowel movements were normal in 14 per cent there were attacks of diarrhea and in another 15 per cent diarrhea alternated with constipation

A history of glossitis was obtained in 65 per cent of the patients In many it was one of the earliest manifestations of the disease Jones and Joyce (1924) suggested that chronic gallbladder disease may be a cause of pernicious anemia but Sturgis and Isaacs doubt this There are many cases of primary anemia without cholecystitis and besides if the digestive upsets were due to gallbladder disease one would not expect to get such prompt relief as usually follows treatment with liver or ventriculin

Achlorhydria was present in all the 150 patients studied Sturgis and Isaacs note that there are two cases in the literature in which free acid is said to have returned after treatment with liver

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W C A

Appendicitis, Acute and Chronic

It is unfortunate today that the diagnosis of acute appendicitis is still not being made often enough and early enough while the diagnosis of chronic appendicitis is probably being made much too often and much too quickly before the patient s problem has been studied with care

Appendicitis appears to be a disease of modern life It does not seem to be common among primitive peoples or even among the more or less civilized nations of the Orient An American physician who practiced for years in Central China never saw a case but when he moved to a coastal city and treated Chinese who were eating the food of foreigners he encountered the disease again

Unfortunately the medical profession does not yet know how civilization brings in its train such troubles as appendicitis It is possible that the present large incidence of this disease is due in part to the fact that for years the operation

cheer up, and about his unwillingness to see old friends or to take any pleasure in work or leisure Strange to say, patient and relatives, having decided that the troubles began with acute indigestion, go to a gastro enterologist and talk to him only about the abdominal distresses The all important story of an injury to the brain has to be dug out of them

It is highly important that the real nature of the illness be recognized in these patients if only to save them from much mismanagement Too often the treatment is begun with the removal of teeth and tonsils, and these shocks only serve to make the patient worse Occasionally they are followed by a more extensive cerebral thrombosis If the physician can only recognize the situation at the start he will protect his reputation by making the correct prognosis and by not promising a cure which is impossible Often it is highly important that the family and business associates be warned that the patient is not likely ever to return to his work The invalid often goes on living for many years, but from time to time another little vessel becomes plugged, there is another attack of dizziness with or without vomiting and each time there is more injury to the brain and with it more change in character more weakness and more mental suffering

Treatment

When the abdominal distress is due to weakness of the heart, much can be accomplished by first putting the patient at rest and giving him digitalis, and then teaching him to live within his limits of strength

When the symptoms are due to cerebral arteriosclerosis and thrombosis, there is little that can be done even in a palliative way Often what is most needed is to give the relatives a better understanding of the problem so that they will be less critical of and more sympathetic with the patient

W C A

The Digestive Disturbances Associated with Pernicious Anemia

The gastro-enterologist must always be on the watch for pernicious anemia because the large majority of the patients with this disease are likely to be seen first by him According to Sturgis and Isaacs who studied the digestive symptoms of 150 such patients 60 per cent showed loss of appetite amounting in some cases to actual aversion for food During remissions, or shortly after treatment is started the appetite usually returns and the patient may even become ravenously hungry

Fifty per cent of the patients had occasional attacks of mild nausea and vomiting Vague abdominal pain was present in about 25 per cent it was

Acute Appendicitis

In spite of about thirty years spent in campaigns of education among physicians and laymen acute appendicitis still exacts too large a toll of life each year Moynihan s rhymed aphorism continues to be ignored

> Purgation spells perforation
> In an appendix kinked and bad
> Food and drink annoy him
> But aperients drive him mad

The statistics of Bower Dixon and others show that half of the patients who die from appendicitis have received a dose of castor oil or some other purgative early in the course of the disease Certainly no physician should ever give a laxative to a patient complaining of abdominal pain until he is sure that he is not dealing with some serious condition such as appendicitis or intestinal obstruction

Another common cause of disaster is the tendency on the part of patients and even physicians to put off efforts at diagnosis and proper treatment Sometimes however the patient or the family or the physician can hardly be blamed for the final disaster because the symptoms of the disease were either mild and confusing or else so fulminant that there was little time or opportunity for any study of the problem Another great source of difficulty is that when perforation occurs the pain often ceases, and instead of becoming more alarmed the patient and the physician feel so reassured that they stop worrying

When called to see a patient in an acute attack of abdominal pain it is always helpful to take a careful history this is especially so when a little questioning reveals that in the past there have been similar attacks and that in one or more of them the attending physician made the diagnosis of appendicitis, or wished to operate

The most important symptoms, and those most frequently seen are pain a rapid soft pulse fever nausea and vomiting Usually pain comes first and not infrequently it is the only symptom during that stage of the disease in which operation can give the best results Sometimes actual gangrene and perforation can be present before either nausea or vomiting appears Often before there is definite fever the physician will be warned that something is wrong by noting an increase in the rate of the heart beat and a softening of the pulse

The pain may come on slowly or abruptly and may last several hours before the patient gives in to it It is often severe and steady and in fully half of the cases it is located in the right iliac fossa Not infrequently and especially in children it is felt first in the epigastrium or midabdomen but as the peritoneal

of appendectomy has been saving the lives of young persons who, if they had been left alone would have died If as often seems probable, there is a hereditary predisposition to the disease, then for years surgeons have been bringing about the survival of persons who are unfit in so far as they have inherited often from both parents a susceptibility to appendicitis

Etiology

The appendix seems to be particularly subject to overwhelming infection because it is a sort of abdominal tonsil, it consists mainly of lymphoid tissue which apparently was designed to serve as a barrier against invasion by bacteria So far as this invasion is concerned the ileocecal region seems to be the weakest spot in the bowel perhaps because its content is richest in living bacteria It is doubtless for this reason that most animals are supplied with a mass of lymph nodes in this region

It is now believed that obstruction of the lumen of the appendix or the presence of fecaliths or other foreign bodies is not essential in the development of appendicitis According to Aschoff anerobic bacteria, and particularly Bacillus welchii are often responsible for the acute forms of inflammation Acute systemic infections must either reduce the resistance of this part of the bowel or else the invading organism which caused the "cold" or the measles or the scarlet fever or the septic sore throat was responsible also for the appendicitis which followed Occasionally also one will find what appear to be small epidemics of appendicitis in families or in persons who are closely associated in business

Recent studies by Collins (unpublished Mayo Foundation thesis) in 60 cases of uncomplicated chronic appendicitis in which the pathologist could demonstrate definite lesions showed that the muscular coat was almost always sterile It was infected in only four cases In 149 cases in which definite chronic appendicitis was associated with other abdominal diseases, there were 30 in which various types of streptococci and colon bacilli could be isolated from the muscular coat

Some physicians go so far at times as to wonder if there ever is such a thing as chronic appendicitis but this isolation of bacteria from the muscle, together with the demonstration of marked histologic changes in the organ, should go far to show that there is such a disease

Age —Appendicitis is a disease of young persons and half of the cases involve children and youths younger than twenty years of age It is less common in infancy but cases have been reported in which the disease occurred in the new born It is unusual in the aged but persons past middle age are not immune

tension of the two rectus muscles one can be fairly sure that peritoneal irritation is present In some cases however, the peritoneal cavity will contain a considerable amount of cloudy fluid at a time when there is little rigidity of the muscles Sometimes it is helpful to palpate the cecum as the thigh is flexed and extended on the abdomen because this maneuver will bring out pain and tenderness In case of doubt it is well always to make a rectal examination because not infrequently the tip of the inflamed appendix can be felt or if rupture has taken place a mass will be discovered The temperature may be between 99 5° and 101° F The pulse is often normal at first but as the peritoneum becomes irritated it usually becomes faster and softer

In every case of suspected appendicitis the physician must carefully examine the lungs because occasionally pneumonia with irritation of the upper surface of the right leaf of the diaphragm will produce the picture of acute appendicitis

Whenever there is any reason to suspect the presence of appendicitis leukocyte counts should be made at short intervals of time If at the first examination the leukocytes are found to number around 12 000 or 15 000 and if two or three hours later the count has gone up to 18 000 or 20 000 there should be no further delay in ordering an operation even if other symptoms and signs are reassuring *Occasionally in elderly patients or in young ones with a virulent* infection the leukocyte count may not rise much but there usually will be a large increase in the polymorphonuclear cells

Examination of the urine is helpful if it shows the absence of pus and blood

Diagnosis —The combination of pain beginning in the epigastrium and shifting to the right iliac fossa tenderness at McBurney's point rigidity of the right rectus muscle nausea vomiting fast pulse fever and leukocytosis should leave little doubt about the diagnosis

Ordinarily indigestion or colic due to the eating of spoiled food or to eating when fatigued or excited is more likely to be associated with a diffuse pain There may be much nausea and vomiting but there should not be any rigidity or localized tenderness and there should not be much if any fever or any decided rise in the leukocyte count If pain is present it is generally mild and bearable Often there will be diarrhea and sometimes the giving of an enema of warm physiologic saline solution will bring a large measure of relief

The pain produced by *a stone in the right kidney or ureter* is likely to come on rather suddenly and to be more severe than that of appendicitis The patient may be in agony with sweat rolling off his body and he is likely to need morphine The pain is usually felt first in the region of the kidney and from thence it radiates into the right testicle or groin The patient may know that he is subject to such attacks and may remark that on previous occasions he has passed gravel There is likely also to be considerable frequency of urination

coat of the appendix becomes involved it shifts to the usual region around McBurney's point In other cases the pain may be diffuse and not well localized in any region of the abdomen

Occasionally the pain will be so sharp and colicky that much time will be wasted in trying to rule out the presence of a stone in the ureter or bile duct Sometimes and perhaps especially when the appendix is behind the cecum and close to the ureter the urine will contain some red blood cells and then even an expert urologist may for a time, be deceived as to the cause of the colic

In some people as the cecum rotates into place during embryonic life the tip of the appendix seems to get caught near the liver and to be held there so that it finally comes to lie retrocecally When such an appendix becomes inflamed the pain may be in the upper right quadrant where it will cause the physician to think of gallbladder disease If, on the other hand, the appendix hangs down into the pelvis the symptoms may suggest the presence of tubo-ovarian disease or even acute cystitis

Sudden cessation of the pain unless it is accompanied by a prompt slowing of the pulse and a drop in the temperature and the leukocyte count, is always a worrisome symptom If the relief is due to perforation of the appendix, the pulse will remain fast, the temperature will go higher, and the patient will continue to look sick

In some patients nausea and vomiting may for several hours, be the most striking or even the only symptoms Occasionally the patient and the physician will be deceived because the acute attack of appendicitis follows a large meal or some dietary indiscretion which might make anyone ill Sometimes it may be found that the bowels have not moved for two days before the attack Such constipation may be either a predisposing factor or a result of the appendicitis In children one of the early symptoms is likely to be diarrhea Not infrequently the patient will report that although the pain and nausea appeared in the morning he or she had spent a very restless night

Fever is always an important symptom if only because it helps so much in differentiating appendicitis from an ordinary stomach ache or severe attack of indigestion Occasionally there will be a chill In elderly persons the fever may be slight or absent while in children it is likely to be high

Physical Examination — In many cases the patient will remain up and about for some time and may even stay at his work High school or college youths will sometimes continue at their games Usually when the physician is called, the sufferer is in bed perhaps on his right side with the right thigh flexed on the abdomen He or she may remark that this particular pain is more severe than anything that has ever been felt before during attacks of indigestion Gentle palpation will usually show tenderness and perhaps some resistance in the right iliac fossa By the time a definite difference can be made out in the

tension of the two rectus muscles one can be fairly sure that peritoneal irritation is present In some cases however, the peritoneal cavity will contain a considerable amount of cloudy fluid at a time when there is little rigidity of the muscles Sometimes it is helpful to palpate the cecum as the thigh is flexed and extended on the abdomen because this maneuver will bring out pain and tenderness In case of doubt it is well always to make a rectal examination because not infrequently the tip of the inflamed appendix can be felt or if rupture has taken place a mass will be discovered The temperature may be *between 99 5° and 101° F* The pulse is often normal at first but as the peritoneum becomes irritated it usually becomes faster and softer

In every case of suspected appendicitis the physician must carefully examine the lungs because *occasionally pneumonia with irritation of the upper surface* of the right leaf of the diaphragm will produce the picture of acute appendicitis

Whenever there is any reason to suspect the presence of appendicitis leukocyte counts should be made at short intervals of time *If at the first examination* the leukocytes are found to number around 12 000 or 15 000 and if two or three hours later the count has gone up to 18 000 or 20 000 there should be no further delay in ordering an operation even if *other symptoms and signs are reassuring* Occasionally in elderly patients or in young ones with a virulent infection the leukocyte count may not rise much but there usually will be a large increase in the polymorphonuclear cells

Examination of the urine is helpful if it shows the absence of pus and blood

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during the attack, and there should be red blood cells in the urine The presence of such red blood cells is not decisive, however, as has already been stated In case of doubt the physician must be careful not to waste too much time in attempts at ruling out the presence of kidney stone, but neither does he want to operate for appendicitis when the trouble is in the ureter

Especially in women and girls acute pyelitis may produce a clinical picture somewhat like that of appendicitis Pyelitis must be thought of particularly in the case of pregnant women Always in such cases a catheterized specimen of urine should be examined for the presence of pus and bacteria In case of doubt a roentgenogram may be helpful if it shows a normal sized kidney shadow with no sign of stone In a pregnant woman an ectopic pregnancy must always be kept in mind

Gallbladder colic is likely to come on suddenly, the pain is more severe and agonizing than that of appendicitis it may be associated with a feeling of difficulty in respiration and the patient is more likely to require morphine for relief In some cases the patient will be found on hands and knees The pain is usually high in the abdomen and it tends to radiate toward the right shoulder blade Commonly it is associated with nausea and vomiting and bloating There is often some rigidity in the upper right quadrant of the abdomen In many cases there is a history of other similar attacks relieved by morphine, and usually the patient has suffered with flatulence and bloating More rarely there have been attacks of jaundice, and a roentgenogram may show the presence of stones

Acute pancreatitis acute perforation of a peptic ulcer and thrombosis or embolism of the mesenteric vessels all are likely to be associated with terrific pain, great prostration and shock

Intestinal obstruction can give a picture somewhat similar to that of acute appendicitis but fortunately the differential diagnosis is not so important because in both cases the best treatment is surgical In cases of intestinal obstruction the physician will sometimes be able to get a history of previous mild attacks in which there was bloating borborygmus with much gurgling, nausea loss of appetite and possibly constipation

Treatment — Perhaps the first essential in the treatment of cases of acute appendicitis is a sufficient degree of conscientiousness on the part of the physician so he will not let matters drift on until nothing curative can be done It is often essential also that the physician through the friendliness and frankness of his demeanor gain the confidence of the patient and the family and that he explain the situation to them so clearly and convincingly that they will accept immediate operation Especially is this true when, as not infrequently happens, the patient has one or more relatives who are Christian Scientists, or who, for various reasons, are opposed to the practice of surgery

Even when the physician sees at a glance that a serious appendicitis is present it often is advisable to spend a little more time on careful physical examination, on getting blood counts and on consultations with other physicians or surgeons. This may not be so necessary when the physician is an old family friend and advisor but it often is essential when the physician is young and previously unknown to the patient and his relative. In many cases a too prompt insistence on immediate operation will only result in the physician's being discharged. The next man who is called if he is more patient and tactful may have little difficulty in getting the patient to the operating room.

Often it is well for the physician to admit that the chances are that if the patient is not operated on the inflammation will subside but if recovery does occur, the chances are that there will be more ill health and more attacks until finally something has to be done. Still more important is the argument that if the process should go on to gangrene of the appendix and peritonitis the patient will then be face to face with several serious possibilities. At best he is likely to be in the hospital for six weeks he will be draining pus for a long time he may develop serious complications due to the spread of infection *through the abdomen and perhaps all over the body he stands a large chance* of losing his life and if he survives he is likely to be left with many adhesions or a diseased gallbladder, which will cause more trouble later. In the case of girls it is well to explain to the parents that a peritonitis is likely to gum up the ends of the fallopian tubes and to glaze over the ovaries so that menstrual difficulties and sterility will result.

Unfortunately, in spite of our present-day knowledge of the subject and the availability in most communities of good surgical facilities the mortality from appendicitis is still far too high. Much of it doubtless is due to the fact that there are so many families who for one reason or another refuse to call a surgeon until they become badly frightened by the progress of the disease.

During the short period of observation of the patient the physician will do well to avoid the use of morphine. If the pain is stopped both patient and physician are more inclined to let matters drift until it is too late for the surgeon to do much in a curative way.

When the physician is satisfied that he is dealing with a case of acute appendicitis, the only right thing to do is to call a surgeon and to send the patient *to the hospital for immediate operation. In those cases in which the physician* is called late and in which it is evident that peritonitis is already widespread the patient had best be placed in the Fowler position and treated expectantly. Nothing should be given by mouth and fluids should be injected into the veins or under the skin. *It may help to wash the stomach out occasionally with a tube.* Enough morphine should be given to control pain. It is questionable if an ice bag or a hot water bottle has any value but if either one or the other is com

forting to the patient, it may be used If, after a time, the inflammation localizes, the abdomen may be opened in order to establish drainage

Chronic Appendicitis

There is no question that there is such a disease as chronic or recurrent appendicitis An attack of acute inflammation in the appendix is likely to leave scars and to predispose the organ to subsequent infection In some cases it may be that the infection is smouldering from the start, and then it may be impossible to get a history of an acute flareup

Unfortunately in a particular case the report of the pathologist does not help the physician much in deciding whether or not he did the wise thing in ordering an appendectomy Signs of past or present inflammation can be found in every appendix and according to some pathologists one can find just as marked changes in a series of appendices removed routinely in the course of operations on the abdomen as in a series of appendices removed because a diagnosis was made of chronic appendicitis

Unfortunately even when the patient recovers and goes on his way singing the praises of the surgeon the physician still does not know whether or not his diagnosis was correct Too often the operation proves to have been useless and ill advised because after an interval of from two to fifteen months, the patient returns just as miserable as he was before

The next question is Can the roentgenologist help in making the diagnosis of chronic appendicitis? Probably few of them would claim that they can, but seeing that their livelihood depends on their ability to satisfy the physicians who send them their work and seeing that most of these physicians crave positive diagnoses it is a rare roentgenologic report that does not contain the suggestion that since the appendix did fill or did not, or emptied too soon or too late or is long or short or is pointed upward or downward it is probably diseased Then it is up to the physician or surgeon to use these statements as he sees fit If he wants to operate he can view them with alarm, and if he does not want to operate he can ignore them

Every thinking physician must admit that there is altogether too much operating done for chronic appendicitis As some wag has said the commonest operation performed in America today for the relief of duodenal ulcer is appendectomy and this same type of treatment is meted out for many other organic and functional diseases of the digestive tract Because of this scandal to the medical profession, many physicians who wish to be honest become so upright that they lean over backward and they fail to turn over to the surgeon some patients who could well be cured by him

There are many patients who come complaining of pain or a slight ache in

the right iliac fossa often they are conscious of something wrong and they are always palpating this region In addition they will have more or less indigestion perhaps a faint suspicion of a hunger pain often a tendency to fill up quickly after meals perhaps some flatulence and belching, and often a good deal of nervousness and a feeling of being dopey and below par If in such a patient, there is a history of one or more attacks of acute pain in the appendix region a diagnosis of chronic appendicitis may be made with a fair degree of certainty Always of course the physician must have tried to rule out the presence of peptic ulcer cholecystitis or serious disease in the colon in the right kidney and ureter or in the right side of the pelvis Many is the woman with a chronic pyelitis who has had the appendix removed without relief

Perhaps the main difficulty the physician faces in attempting to make a diagnosis of chronic appendicitis is that of deciding how many of the complaints can be ascribed to the patient s nervousness and hypersensitiveness and general constitutional inadequacy Always the surgeon must avoid operating unnecessarily on patients with migraine mucous colitis food allergy and even ordinary constipation

Often it is essential that the physician have enough clinical sense and experience to say All those symptoms could not be produced by chronic appendicitis even granting that the disease is pre ent Actually it probably would be much better for the mental and moral development of physicians if in those cases in which no history can be obtained of an acute attack of pain n the right lower quadrant of the abdomen operation for the removal of the appendix should be called an exploration and not an operation for the rel ef of chronic appendicitis The removal of the appendix in cases in which there never has been an acute attack of appendicit s must aw ys be a gamble with the odds considerably against the patient and against the correctnes of the diagnosis Such an operation should never be done until every other po b l ty has been considered and until everything pos ible has been done to ru e out the presence of other disease which could explain the symptoms Occasionally pain n the region of the appendix i due to spondylitis with irritation of some of the nerves supplying the iliac region At other time sacro-iliac strain will be responsible for at least some of the disturbances complained about Other pos ible causes will be found described in the section on pseudo-appendicitis

Before operating it is often well then to see what can be done by regulating the patient s diet and by keeping the colon empty with mild methods such as enemas of physiologic saline so ution In all cases of doubt it is well for the patient to spend a few weeks on an elimination type of diet This is especially true if the patient or members of his family give a history of asthma hay fever or hives

As has been pointed out if operation is performed the patient is likely to

be relieved of his or her symptoms for a few months, but if the disease was not appendicitis, sooner or later the symptoms return, and then it is realized that the cause of the trouble is yet to be found

If an appendix is sufficiently diseased to produce muscular spasm in the lower end of the ileum there should be some ileal stasis, and actually, in a few cases such stasis is present and definite in most others the sign seems to be of little value Some laboratory workers have reported an increase in the number of large mononuclear cells in the blood in cases of subacute appendicitis, but, again the sign cannot be trusted

There is no question that occasionally a thoughtless and not overly scrupulous surgeon will cure a patient who was refused operation by a far more enlightened and conscientious colleague, but the true physician does not want to operate needlessly on perhaps ninety seven patients in order to get a spectacular result in the remaining three That appendectomies are being performed needlessly and without sufficient care can hardly be denied by anyone who sees a large amount of clinical material If we appear to speak feelingly on the subject it is because in so many cases in which the problem is later reviewed, it seems so obvious that if the surgeon had only made a cursory examination of the patient before operation or if he had made the ordinary roentgenologic or laboratory examinations or if he had at operation realized that he really had no more reason to be operating on the appendix than on any other organ in the abdomen he would have made a larger incision and then up around the gall bladder or stomach or down in the pelvis he would have discovered much important work to do

In all puzzling cases then the conscientious physician will see to it that his patient is thoroughly examined before and not after appendectomy

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Pseudo Appendicitis

Not infrequently after listening for a few minutes to a patient s story, the gastro-enterologist will say to himself Well this will be easy what a typical

story of recurrent appendicitis and then he discovers to his disgust, that the appendix has not only been removed once but a second and perhap even a third fruitless exploration of the right iliac fossa has already been made Often after such operations there is relief of symptoms for a while but usually after from three to nine months, the pain or burning is back again

Often the pain over the cecum comes every day or the patient is always conscious of this region and is always trying to reach down and hold something in place Sometimes there are no symptoms of indigestion such as one would expect to see if the appendix were diseased but often there is flatulence constipation, and perhaps nausea heartburn belching and a feeling of autointoxication

Years ago Connell reported 87 such cases 48 of which were from his own practice He found that one patient in four operated on for chronic appendicitis did not recover There were five women to one man which strongly suggests that the disease is functional in origin As E V Allen has shown (1933) organic disease generally affects two or three times as many men as women while functional troubles attack many more women than men

In 16 of the patients the pain was continuous in 23 it came in severe attacks and in 26 it came in mild attacks In 23 there was abdominal tenderness, in 39 hypersensitiveness in 20 a side ache and in 14 a burning sensation The location of the pain varied markedly in different persons In many cases it was in the right lower quadrant but in others it was in the epigastrium or around the navel and in a few it was on the left side also Usually the pain was worse on exertion

Fifty two of the patients complained of nausea 24 of vomiting and 58 of indigestion and gas Twelve had slight fever and 2 of these later were found to have tuberculosis Fifty four were constipated and 24 had normal bowel movements In 7 diarrhea alternated with constipation and in 2 diarrhea was constant

Sixteen complained of frequency of urination 28 of the 73 women suffered with dysmenorrhea and 33 of the patients were neurotic or hysterical or had spasms and fainting spells Seven were air swallowers Twenty nine complained of neurotic pains elsewhere in the body There was a family history of similar abdominal troubles in 13 patients

At the first operation some fault could be found with the appearance of the appendix in all but 6 cases Enlarged mesenteric nodes were found in 9 cases Symptoms returned within six months in 39 cases and in between six and twelve months in 7 In the other 21 cases the trouble returned after a few years usually after the patient had been subjected to marked psychic strain

Subsequent operations on 19 patients failed to show much that could explain the symptoms except possibly cholecystitis in 4 and enlarged lymph

nodes in 7 At the second operation adhesions were either broken up, or else new ones were made with the idea of suspending a movable cecum or stomach The results of this second operation usually were as bad as those of the first

I can remember a case in which the patient succeeded in having herself operated on four times in two years She was then annoyed because the surgeon balked at further exploration of the abdomen When placed in the hospital for a few days of observation this young woman gave several remarkable exhibitions of major hysteria and the presumption is that all her troubles were due to some queer mental twist It is probable that in other cases like this the patient's pain and desire for mutilation are manifestations of a psychopathic personality

In other cases the essential factor is a constitutional inadequacy with its often associated hypersensitiveness of the colon and all parts of the nervous system In these people it may be that fatigue and strains of various kinds are sensed as pain and focused here and there about the body as in the head, the epigastrium the right lower quadrant of the abdomen, the lower back or the pelvis

In other cases the pain is due apparently to a typhlitis, brought on by constipation and the resultant stagnation of feces in the cecum In other cases it is but a part of the pain felt throughout the course of a hypersensitive colon

When the pain is associated with ileal stasis and with symptoms of back pressure in the small bowel such as nausea vomiting and a feeling of fulness immediately on eating it is probable that there is some form of inflammation in the bowel or in the mesentery in the region of the ileo-cecal sphincter, some lesion that causes spasm in the sphincter and with this an interference with the passage of food residues from the small into the large bowel In one such case reported by C H Mayo and me a permanent cure was obtained with the help of an operation which short circuited the sphincter

In other cases it will be found by pinching the skin and abdominal fat that the sensitiveness is superficial and then the physician will think of a lesion of sensory root ganglia due perhaps to infection with a herpetic virus or with the same organism that produced the severe spondylitis so noticeable in roentgenograms of the back In the case of one such patient seen by me, four fruitless abdominal exploratory operations had been performed in three years The man's skin was covered with neurofibromata and the probability is that one of these was growing on one of the sensory nerves leading out of the right side of the abdomen Occasionally one can find the scars of herpetic blisters on the back

In many cases symptoms of indigestion continue after appendectomy because the diagnosis was wrong and the patient was and is suffering with duodenal ulcer or cholecystitis If the surgeon had only made a larger incision and had

passed his exploring hand around he would have been astonished to find how much disease there was in the upper part of the abdomen

In many more cases the distress on the right side of the abdomen is but a part of that produced by a hypersensitive colon Unfortunately when the appendectomy fails to bring relief there is a marked tendency on the part of the patient and his medical advisors to assume that adhesions have formed and that an operation for their removal is indicated and necessary Actually the more experienced gastro-enterologists and surgeons in the world today are inclined to distrust the diagnosis of adhesions and they rarely ascribe symptoms to them even when they know that they are present

In many cases it seems most probable that there is some organic cause for the pain or burning and for the associated severe indigestion but what it is no one as yet can say Because so many of the patients are neurotic and hypersensitive because many have queer aches and pains elsewhere in the body and because few of them ever come to any bad end even after many years of complaining it is most probable that the cause is a functional one and that the nervous system is at fault

In all cases of unexplained pains in the abdomen the physician should keep in mind the fact that headache or facial neuralgia is a very real disease and surely no one who has suffered with severe migraine or tic douloureux would ever for a moment entertain the suggestion that the pain is imaginary And yet at necropsy the pathologist is rarely able to show anatomic changes that would seem adequate to explain the torture suffered by the patient during his lifetime Since there is no reason to assume that the sensory nerves of the abdomen are immune to such obscure diseases I think we physicians must be careful never to deny the existence of a pain in the region of the stomach or colon or gallbladder simply because we cannot find a gross anatomic change to explain it

Diagnosis

It is a good rule to avoid the diagnosis of chronic appendicitis unless the patient has had at least one attack that strongly suggested the presence of acute inflammation in the appendix The next good rule is to avoid operations of all kinds on patients who are constitutionally inadequate psychopathic neurotic migrainous allergic or otherwise abnormally sensitive It is a good rule also to avoid operations on all persons who complain for years of aches and pains all over and particularly on persons whose disability is out of proportion to the amount of disease that can be found or suspected Furthermore an operation should never be prescribed wholly or largely on the basis of a roentgenologic diagnosis of appendicitis When an operation is performed

on the chance that the appendix is chronically diseased, a right rectus incision should be made and the abdomen should be explored so carefully and thoroughly that if the result is poor, the patient can at least be spared a second trip to the operating room

Treatment

Every effort should be made to keep the colon clean for two or three weeks with enemas of physiologic saline solution to see if this will help A smooth type of diet may also help If the patient is in bad shape nervously, a rest cure and a certain amount of psycho therapy may put a stop to the pain or else make it more bearable In the worst cases one might try the effect of blocking spinal roots with novocain If the result were striking an operation on the same roots might be considered In some cases in which there is a suspicion of the presence of a peptic ulcer an ulcer type of treatment may be tried Occasionally a moderate dose of roentgen rays applied to the spinal roots will bring relief

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W C A

Pseudo Peptic Ulcer

For every person seen with a definite peptic ulcer there is another one with symptoms which are similar but in whom an ulcer cannot be found at surgical exploration or at necropsy In many of these persons the hunger pain is typical but in others there is something suspiciously wrong about it Perhaps it is more a burning than a pain or it is not well relieved by food, or it comes sometimes before breakfast or it does not waken the patient at night What is often most suspicious is the fact that the distress has been continuous for years, sometimes the patient says 'I haven t had a day s freedom since this trouble began" With a typical ulcer and at least in the first few years, the symptoms should come in attacks with intervals of complete relief in between

The patients with pseudo ulcer are temperamentally much like those with severe and intractable duodenal ulcer Like them they often have a very high gastric acidity and a very high concentration of pepsin Rarely, one of these patients will bleed severely from some undiscoverable point in the upper digestive tract

When the history is atypical and an expert roentgenologist reports that he cannot see an ulcer, the surgeon usually will do well to stay his hand, and save

himself from the chagrin later of being unable to demonstrate a lesion to those who stand, watching around the operating table Occasionally, the roentgenologist s report of deformity in duodenum or stomach will cause the clinician to give up his really correct diagnosis of pseudo ulcer and just as often the negative report of the roentgenologist will cause the clinician and the surgeon to refuse operation to a patient who sorely need it Even the surgeon with the duodenum and stomach between his fingers will occasionally fail to detect a large ulcer perforating posteriorly or he will cut out a piece of duodenum which feels wrong to him but looks normal to the pathologist who receives it

Because of these mistakes some physicians have been led to wonder if a more careful search might not show a lesion in the case of every patient with severe symptoms of ulcer I am fairly certain it would not because I have seen cases in which the stomach and duodenum were opened and carefully explored by the surgeon and I have seen a few in which the examination was later conducted more extensively by the pathologist and an ulcer was not found

What then is the lesion? No one knows In many cases the stage would seem to be all set for the development of an ulcer there is the nervous temperament the strenuous harrassed life the meals eaten hurriedly and absentmindedly and the overly powerful gastric juice and yet for some strange reason a number of these patients whose course I have watched for years do not seem yet to have developed a real ulcer The mechanism of the production of symptoms may be similar to that in the case of actual ulcer Perhaps the mucous membrane of the stomach becomes so sensitive that it can react painfully to the presence of the acid gastric juice No one knows

Treatment

The first and most important thing is not to operate on these patients because an optimistic gastroenterostomy is likely to do more harm than good These people are helped most often by rest short vacations sedatives and food taken between meal Those who smoke too much must try to reform and every effort must be made to secure peace before during and after meals Fifteen minutes of rest before a meal and a half hour s rest afterward will sometimes work wonders In a few cases the relief of constipation will also help greatly

W C A

Pseudo Cholecystitis

For every case of true cholecystitis or cholelithiasis seen by the clinician there is another one in which the symptoms are similar and perhaps severe but

in which not only does the gall bladder show up perfectly in the cholecystogram, but cholecystectomy does not bring permanent relief

Some of the possible causes of this syndrome such as constitutional inadequacy spondylitis and the infection of intercostal nerve ganglia with a herpetic type of virus have already been listed under the heading of pseudo appendicitis Occasionally the soreness can be located definitely in the abdominal wall, and then the lesion is probably in the nervous system In some cases the patient is so psychopathic or neurotic that it is hard to know how much faith to put in the story but in the large majority of instances the symptoms must be accepted as real and due probably to some organic cause Not infrequently the attacks of pain will be associated with objective signs such as fever, slight jaundice diarrhea dark or clay colored stools and an extremely tender liver In many cases the symptoms are those of severe cholecystitis with the typical flatulence and bloating after supper, and even typical colic with the usual radiation to the right shoulder blade

In such cases exploration of the abdomen, even during a severe attack does not throw much light on the condition The wall of the gall bladder, although histologically normal will sometimes be found to be full of streptococci or other virulent organisms Its removal may give complete relief for a year or so, and then the symptoms return Usually the edge of the liver will be rounded and an excised section will show signs of hepatitis The lymph nodes along the common duct may be enlarged, and there is sometimes an enlargement and thickening of the head of the pancreas together with signs of old peritoneal inflammation about the cleft of the liver In other cases, with the severest symptoms the surgeon may be puzzled at his inability to find any sign of inflammation anywhere in the right upper quadrant of the abdomen

What then is the cause of the trouble? It seems as if it must be some disturbance in liver function due perhaps at times to infection and at other times to metabolic disturbances or to poisoning by some substances arriving by way of the portal circulation One must think also of a failure to excrete bile along biliary capillaries or ducts, blocked by a swelling of the lining epithelium Sensory nerve endings might conceivably be irritated either by chemical substances formed in the liver by spasm in the blood vessels (which carry in their sheaths most of the sensory nerves), or by distention of the capsule of the liver

One argument against the theory that the disease is due to hepatitis is to be found in the fact that ordinarily the patient with a badly hobnailed but still "compensated" liver does not complain much if at all of symptoms resembling those of cholecystitis In favor of the hepatic theory is the fact that in one of my cases in which much relief was obtained from the insertion of a T tube into the common duct, when typical attacks of pain, soreness, slight jaundice, in

toxication nausea, flatulence and diarrhea recurred they were ushered in by a lessening of the flow of bile and a change to a black viscid and ropy type of secretion Associated with this change there was fever which suggested the presence of infection Immediately after a severe attack the Rowntree Rosenthal test failed to show any defect in liver function, but in the absence of widespread destruction of the liver this was not surprising In this particular case exploratory operations failed to show anything wrong in or around the liver to explain the severe and disabling disease which has been present off and on for many years

Treatment

In the absence of an understanding of the disease it is difficult to do much for most of these patients All one can do is to treat them much as if they had cholecystitis. Occasionally prolonged drainage through a T tube will bring relief, and sometimes the symptoms disappear for a time following a Carlsbad cure or a course of Lyon biliary drainages In many of them the type of food eaten does not seem to make much difference in the symptoms and one cannot hope to relieve these patients with any type of diet now known to science Sometimes the restriction of fats helps and almost always the patient can have a more comfortable evening and a better night s sleep if he or she will eat a small dinner and shift the heavier meal to midday

Theoretically, an increase in the rate of flow of the bile should help some of these patients, but actually the use of decholin, which acts as a strong cholagogue has been disappointing

If the trouble is due to a smoldering infection, then some of these patients might be helped by the sort of treatment that is used in cases of tuberculosis The difficulty is to get them to try it

As time goes on it may be that the neural surgeon will give some of these persons relief at least from pain by section of the two or three sensory roots on the right side that carry the fibers from the liver Unfortunately one cannot hope for much help from this operation when the symptoms consist mainly of nausea bloating, fever and a feeling of intoxication

W C A

INTESTINAL OBSTRUCTION

Obstruction may be simple or it may be complicated by strangulation of the bowel In the case of simple obstruction all that has happened is that some barrier has formed which keeps the intestinal contents from moving onward If this obstruction is promptly removed no serious injury will take place either

to the gut or the patient If it is not removed, the bowel becomes more and more distended its blood supply is likely to be impaired, and from this there may follow gangrene perforation and peritonitis

When strangulation of the bowel enters into the picture, the symptoms are usually much more stormy than when the obstruction is simple There are at least two reasons for this one that reverse peristalsis is set up, and the other that a severe toxemia appears This is most marked when the barrier is in the upper part of the small bowel When the gut is injured and strongly stimulated powerful waves of reverse peristalsis are sent off orad to produce violent vomiting In such cases food or liquid given by mouth may be unable to leave the stomach and certainly it will be unable to approach the point of obstruction When on the other hand a barrier forms quietly, as it often does in the case of an intestinal carcinoma the muscle around the growth is not stimulated and there is little if any tendency to start up reverse peristalsis As a result food residues can come down to pack up against the obstruction

As already pointed out a serious feature of jejunal obstruction due to strangulation of the bowel is the early appearance of a severe toxemia In spite of the large amount of experimental work that has been done on the problem not all workers are agreed as to how this toxin is formed, what it is, and how it gets into the blood There are many reasons however, for believing that it is formed by a breaking up of protein in the mucous membrane of the bowel whenever this is injured The formation of the toxin may be accelerated by the presence of bacteria but their help is not necessary This is shown by the fact that the toxemia is worst when the almost sterile upper jejunum is involved and mild when the highly infected terminal ileum or colon is blocked The poison produced in the strangulated loop of jejunum seems to be very similar at least in its action to that formed in cases of acute pancreatitis bilateral adrenalectomy and anaphylactic shock Strange to say, this toxin is not absorbed from the normal mucous membrane of the bowel

There are reasons for believing now that in high intestinal obstruction there are two definite processes involved in the production of the toxemia First, there is a disturbance in the acid base relationship in the blood, with loss of chlorides and the development of alkalosis and dehydration Much the same picture can be produced if gastric juice is lost from the body either through excessive vomiting or through a fistula Normally the chlorine secreted in the gastric juice appears to be reabsorbed only in the lower part of the small bowel, and apparently this important reclamation of an essential constituent of the body is beyond the powers of the upper part of the jejunum

As one might expect from this much can be done to overcome the intoxication of high intestinal obstruction by the intravenous injection of solutions of sodium chloride It is essential to maintain the level of body fluids, but the

giving of water alone will not save life In many cases pancreatic and biliary secretions are also vomited or impounded and this loss of valuable bases and other chemical substance may well play a part in the serious poisoning which follows

Both in animals and in man the toxemia shows itself by changes in the chemical constituents of the blood the level of urea rises the amount of plasma chloride falls and the carbon dioxide combining power of the plasma is increased

It is possible that some of the shock that is associated with high intestinal obstruction is due to the injury resulting to the nervous system when the bowel struggle powerfully and incessantly to empty itself When obstruction takes place in the more sluggish lower part of the bowel there is much less of this type of activity

With obstruction in the upper part of the small bowel the principal symptoms are likely to be nausea vomiting and toxemia the clinical course will be stormy and if relief does not soon come the patient will die With obstruction in the distal part of the small bowel and particularly in the colon the toxemia if present at all will be slight and the principal danger to the patient will be that of perforation and peritonitis Only rarely can one demonstrate change in the blood in cases of slowly developing obstruction of the colon

Acute Obstruction

The mortality attendant on intestinal obstruction seems to be almost as great now as it was forty years ago Thus the mortality rate published by Kirschman in 1889 was 65 per cent in 1000 cases reviewed by Gibson in 1900 it was 43 per cent and in 1 089 cases collected by Van Beuren and Smith in 1925 it was 42 per cent Some of the reports in the literature indicate rates lower than this but other unreported experience would probably raise the average

The important factor in lowering this tremendous mortality rate will probably be not so much an improvement in surgical technic as an improvement in the knowledge of physicians which will cause them to make the diagnosis more promptly Too many of them are still waiting for fecal vomiting to appear and for the bowel to become gangrenous C H Mayo once stressed the point that death seldom results from exploration but it often results because the exploration was made too late There is no question that the essential factor in saving life is an early operation Thus Tuttle found in a series of 13 cases in which the patients were all operated on within six hours that there were no deaths but in another group of 99 in which the symptoms were allowed to run on for from four to six days the mortality was 37 per cent

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bowel under 'fiddle string' or band like adhesions or in holes in the mesentery Occasionally when a surgeon at the time of a gastro-enterostomy is not sufficiently careful in fastening the edges of the rent in the mesocolon to the stomach and bowel a hole is left through which most of the small bowel will later pass and become caught The symptoms are not acute they are difficult to understand the roentgenologists rarely can see what is wrong and the cause of the trouble is found only at operation

Probably too much stress is laid by the average physician on the dangers of post operative adhesions It is remarkable how many closely binding adhesions can be found at operation or necropsy in persons who never made any complaint of indigestion or constipation Occasionally when a loop of bowel gets caught under a band of adhesions it slips out again and the symptoms of obstruction cease suddenly only to reappear after a few days or weeks Finally some day the pinched loop will become so edematous that it cannot slip back and an operation will have to be performed

The next most common cause of intestinal obstruction is some form of stricture of the bowel of either inflammatory or neoplastic origin Hyperplastic tuberculosis is generally found in the last foot or two of the ileum but occasionally there will be one or more constricted and thickened areas in the upper part of the small bowel The next most frequent type of inflammatory obstruction is found in the colon where it is a sequel of chronic ulcerative colitis Syphilitic strictures are extremely rare

Diverticulitis generally produces an obstruction of the descending colon or sigmoid flexure which is rarely complete Benign tumors of the small bowel are rare Especially when they are located in the small bowel they are likely to serve as the head of an intussusceptum Sometimes when they are located in the last coil of ileum they are forced through the ileocecal sphincter and into the large bowel

Malignant tumors of the small bowel are rare They constitute only one per cent of the cancers in the whole digestive tract Perhaps the commonest is the carcinoid tumor which may be single or multiple Cancer of the large bowel is a common cause of chronic incomplete obstruction which finally becomes acute and complete

Intussusception represents a telescoping of a segment of bowel into the part immediately caudad It is one of the commonest causes of acute intestinal obstruction in children Actually over 50 per cent of all cases occur in children under 10 years of age The commonest type of intussusception is the one in which the last ileal coil goes through the ileocecal sphincter into the colon Next comes the type in which only the ileum is involved and next is the type in which only the colon is involved

Volvulus is most commonly seen in adults after the age of 50 years The

Causes — The following list will give some idea of the various types of intestinal obstruction and the frequency with which they occur

1 External obstruction due usually to strangulation of the bowel in an inguinal or femoral hernial opening
2 Internal obstruction due to
  A Strangulation by
    1 Adhesions either immediately or long after operation, or after some type of peritoneal inflammation
    2 Remains of the vitelline duct
    3 Herniation through
      a Openings in the mesentery
      b The foreamen of Winslow
      c The rent in the mesentery made at the time of gastro enterostomy
      d A congenital or acquired defect in the diaphragm
    4 Incarceration of the bowel in the peritoneal fossæ
    5 Torsion of the omentum mesentery or mesocolon
  B Strictures
    1 Neoplastic { benign / malignant
    2 Inflammatory and due to
      a Tuberculosis usually of the hyperplastic type
      b Chronic ulcerative colitis
      c Pyogenic granuloma usually secondary to appendicitis
      d Syphilis
      e Diverticulitis
      f Chronic granulomas of poorly understood origin often in the last loop of ileum
    3 Congenital in origin
  C Volvulus usually of the sigmoid loop of the colon
  D Intussusception commonest in children but in adults due sometimes to the presence in the bowel of a tumor
  E Abnormal contents of the bowel foreign bodies gall stones
  F Paralytic ileus
  G Dynamic ileus contraction rings of unknown origin
  H Vascular injuries thrombosis and embolism of the mesenteric vessels

Strangulated inguinal or femoral hernia is still the most frequent cause of acute intestinal obstruction Fortunately laymen are gradually becoming educated to the point where they will have hernias repaired earlier in life and where they know some of the danger signals which should send them quickly to a surgeon As is well known the greatest danger comes with the small hernias which are likely to slip out and get caught

The most common cause of internal obstruction is strangulation of the

functional spastic types of obstruction The patients generally are neurotic women who suffer with attacks of bloating and severe constipation Not infrequently the signs of obstruction are so menacing that the patient is operated on Usually nothing is found to explain the condition but occasionally one or more narrowed segments will be found in which there is marked contraction of the muscle Not infrequently such contraction rings are found in children who show symptoms of obstruction Often when the abdomen is open if the narrowed segment is handled the contraction lets go and the patient is relieved In other cases relief comes only when the affected piece of bowel is resected

Symptoms of Acute Intestinal Obstruction — The symptoms have been well described by Wangensteen whose writings on the subject will be quoted freely

In some cases it is possible to obtain a history of other attacks similar to the one seen by the physician but in others the trouble comes out of a clear sky without any warning At first there may be crampy intermittent pains which gradually become more severe and more frequent Later and especially if the obstruction is in the small bowel there will come nausea and vomiting Abdominal distention usually appears still later when peritonitis has developed The temperature will be normal at first later it may be subnormal or slightly raised Early in the attack there is usually some quickening of the pulse later, if the obstruction continues the pulse will be very rapid and weak and signs of circulatory collapse will appear Finally the patient will be cold and will show the pinched and worried look that is so characteristic in cases of general peritonitis The mind usually remains clear until near the end when delirium and coma may announce the approach of death

The quietness or storminess of the symptoms depends largely on the presence or absence of strangulation and injury to the bowel Thus when the blockage is due to a carcinoma or a peritoneal band which does not greatly interfere with the circulation the intestinal contents are likely to come down and pack against the barrier the patient is not very ill and nausea and vomiting appear late When however the blockage is due to a lesion which strangulates the bowel and thereby injures and greatly stimulates the muscle nearby there will soon be so much reverse peristalsis that the intestinal contents will be held back in the upper part of the bowel and even in the stomach severe vomiting will soon appear and the loss of fluid from the body will be enormous

The patient with a strangulated loop of bowel is soon acutely ill At first the pain is likely to be intense and agonizing the temperature may rise from one to three degrees Fahrenheit and the pulse will be greatly quickened If the circulation to a fair sized segment of bowel is impaired symptoms of collapse may soon develop Nausea and vomiting will appear early and they are likely to be severe

As is well known the course of the disease is much more stormy with ob

main predisposing cause seems to be a long mesocolon For this reason the accident takes place most commonly in the sigmoid flexure Occasionally the cecum is affected

Obstruction may be due to foreign bodies such as removable bridges, coins and fruit stones A coiled mass of round worms will occasionally occlude the lumen of the small bowel Enteroliths are rare in man Occasionally a large gall stone will ulcerate through into the bowel to produce blockage of the last coil of ileum When a large foreign body gets into the small bowel, it practically always stops at a point several centimeters orad to the ileocecal sphincter As Alvarez has pointed out this is probably due not to any particular narrowness of the lumen at this point but to the fact that this represents the lower end of the gradient of forces in the small bowel From this point to the sphincter the gradient is probably uphill That this is the explanation is strongly suggested by the fact that complete intestinal blockage in this segment can be produced by the accumulation and agglomeration of a mass of small particles such as those which make up bran

Not infrequently the eating of indigestible foods with coarse residue will bring about complete intestinal obstruction in cases in which there already existed a narrowing of the bowel due to a neoplasm or some form of inflammation. For instance we have seen cases in which a piece of lettuce or a bean served to plug the small hole left in an annular carcinoma of the colon Unabsorbable powders such as bismuth or barium sulfate or magnesia, will occasionally produce a dense mass which has to be dug out of the rectum or from the bowel immediately above an obstructing lesion Impaction of feces occasionally produces obstruction the symptoms of which are not severe

Paralytic ileus is most commonly seen after gastric and perigastric operations and sometimes after operation on the pelvic organs or the kidney It may appear following the removal of ascitic fluid during the course of pneumonia with renal or gallbladder colic and occasionally in cases of heart disease Apparently much of the bowel is so paralyzed that nothing can go through it

Occasionally after operations loops of bowel throughout the abdomen become stuck together for reasons that are not known, and there results what has been called an adhesive type of obstruction In some of these cases the symptoms are mild and it looks for a time as if the patient were going to overcome the difficulty without operation

In other cases the intestinal paralysis is associated with peritonitis In this case, experiment has shown that the quietness of the bowel is not due to injury to the muscle but to inhibition by way of the splanchnic nerves It is doubtless for this reason that the induction of spinal anesthesia sometimes causes the bowels to move

In another place in this chapter there is a discussion of the apparently

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struction in the upper part of the jejunum than with obstruction in the ileum or colon. Sometimes however, volvulus of the sigmoid flexure will be associated with violent symptoms. With obstruction in the lower part of the bowel vomiting is likely to come late and it may not be severe. There are cases in which for a time the only symptom is nausea. Before long there is likely to be a fecal odor to the vomitus even in cases in which the obstruction is in the small bowel. Often also, the material vomited takes on the color of chocolate. In some cases there is a fecal odor to the breath and foul smelling material can be washed out of the stomach several days before fecal vomiting sets in.

Constipation may be present but often and especially at first, the disturbance in the bowel sends off waves both ways, and as a result there is not only vomiting but also griping and tenesmus with the passage of bloody mucus. At the onset of an attack of obstruction in the small bowel one would rather expect the patient to have one or more fairly normal stools.

In the case of post operative obstruction from any cause, the first thing noted by the surgeon will probably be that the patient doesn't look right, he or she is subdued somewhat anxious and states that the upper abdomen feels full as if the stomach were not emptying. There is no appetite and little desire to put anything into the stomach. There may be a little regurgitation, and the pillow may be soiled during the night. Examination will show that the pulse is soft and rapid and the hands moist. There often is some succussion sound as the abdomen is palpated and there may be a little distention.

Soon there is likely to be a fall in blood pressure, the urinary output will decrease and on passing a stomach tube a large amount of fluid will be obtained. Perhaps there will be some inability to pass gas. Later there will be vomiting and the blood will become concentrated as shown by an increase in the amount of hemoglobin and in the number of the cells. An increase in neuromuscular irritability may show itself by a twitching of the muscles and perhaps even by the appearance of tetany.

If the obstruction is a mechanical one there may be pain and audible peristalsis. If the trouble is due to a paralytic ileus sounds cannot be heard even with the help of the stethoscope.

Physical Examination. — This should include first a careful inspection of all places in which an external hernia can form. In stout women particular attention should be paid to the condition of the femoral rings. Ordinarily there are no localizing signs which will help the physician in locating the obstruction in any particular part of the bowel. A rectal examination and in women, a vaginal examination should always be made.

Auscultation of the abdomen will give some idea of the amount of peristalsis present. In the early stages of the obstruction, loud bubbling and tinkling sounds may be heard. Later these sounds may disappear, and an ominous

silence will indicate that peritonitis is present Peristalsis is often visible in cases of subacute or chronic obstruction but it is seldom seen in the presence of an acute obstruction

Roentgenologic Examination — As soon as the patient can be gotten to the hospital a film should be made of the abdomen because this may give information of great value The roentgenologic picture of an obstructed loop of small bowel with the lattice like shadows is so striking and characteristic that no one should miss its significance When the obstruction is in the left half of the colon the right half may be seen to be filled with ga and fluid

In all case of intestinal obstruction the giving of barium is contraindicated because it may make matters worse If there is no sign of a dilated loop of small bowel and if no obstruction can be found in the rectum a barium enema may be given in the hope that it will show a lesion in the colon

Data Secured from the Laboratory — In the early stages of obstruction the leukocyte count should be normal Later it may go up depending largely on the presence or absence of dehydration as well as on the development of peritonitis Changes in the chemical constitutions of the blood plasma ordinarily do not appear until the patient has vomited for a day or two Hence it is that the physician must not wait to make a diagnosis until the laboratory workers can come to his help This is particularly true after operations when the diagnosis of serious trouble must be made by the surgeon largely from the appearance of the patient and the feel of his pulse The hunch or the conviction of the experienced surgeon that things are going wrong is of more importance than a report on the blood chemistry Furthermore changes in the chemical constitution of the blood are usually absent in cases of obstruction low in the bowel

Diagnosis — As Wangensteen says Simple obstruction closely simulates colics that are unattended by physical findings Obstruction due to strangulation must be differentiated from every type of abdominal colic that produces tenderness and rigidity of the abdominal wall What this means is that whenever the physician is called to see a patient who has severe colic with nausea and vomiting he must think of intestinal obstruction and must keep the patient under observation until it is clear that the danger is over In too many case death results from the tendency of the physician to say Oh you've eaten some food that has disagreed with you take a do e of castor oil and you'll be all right The physician then goes off to other patients and when next he is called to see the one with colic, it is too late to save life

It may be helpful in some cases to know that some food was eaten which made other members of the family ill Diarrhea is more likely to be present with an enteritis than with obstruction of the bowel Distention is more likely to appear in the presence of obstruction than with an entero-colitis Gurgling

sounds may be present in both entero colitis and obstruction but the more highly pitched tinkling sounds are not likely to be present with enteritis Especially when the pain is in the right iliac fossa, appendicitis must be thought of If the patient is subject to attacks of giant urticaria, one must think of an allergic form of intestinal upset or Quincke s disease Similarly if there are small hemorrhages in the skin the physician will think of purpura

Gall stone and renal colic may simulate obstruction of the bowel and may be associated with a certain amount of paralytic ileus, but usually the location and radiation of pain and the fact that it was violent from the start should point to the correct diagnosis If the patient is a woman, the physician may have to think also of tubo-ovarian disease ectopic pregnancy and pyelitis As already stated a pelvic examination must always be made and the urine must be examined The presence of a considerable degree of leukocytosis points more to the presence of an inflammatory disease than to obstruction

With acute pancreatitis the onset of the illness is often abrupt the pain is intense and signs of shock soon appear The pain of pancreatitis is likely to radiate directly to the back Torsion of an ovarian cyst occasionally will produce fulminating symptoms With all these lesions the most important diagnostic point may be the absence of those gurgling bubbling and tinkling noises which one would expect to be present with intestinal obstruction

Some neurotic women may present a striking picture of pseudo ileus with severe constipation and tremendous distention of the abdomen, but in these cases the experienced physician will be struck by the fact that the patient is not ill in spite of all her complaining she looks well Roentgenologic examination of such patients fails to reveal any dilated loops of bowel, and if gas is present it is likely to be in the colon Some of it may be in the stomach

Treatment of Acute Obstruction — In all cases in which there is any suspicion of obstruction the patient should be seen at frequent intervals by both the physician and the surgeon It must always be remembered that a failure to take the problem seriously and a willingness to wait indefinitely for the classic signs of obstruction in its terminal and hopeless stages, have caused the death of innumerable patients Certainly the physician must not wait until fecal vomiting appears

Whatever happens purgatives must not be given They are likely to convert a mild obstruction into a fulminating one, and often they take away what little chance of recovery the patient has

Enemas may safely be given and with them it may be possible to empty the colon or at least that part of it which lies below an obstruction It must be remembered that the passage of gas and feces does not rule out the presence of obstruction It has been shown experimentally that even after the bowel has been cut across and the ends closed enemas will bring gas just so long as

some is present in the distal segment, and similarly in the case of high obstruction in man, gas may continue to be passed so long as enemas are given. Sometimes also a small amount of fecal material will get past the obstruction or will be voided from the bowel distal to it

Morphin should not be given until the diagnosis is established. The drug will not entirely stop the peristaltic rushes that produce the gurgling sounds but it can dull the pain, and this may make the physician more inclined to procrastinate and to let the patient go on until the bowel is gangrenous. Especially when vomiting is severe the giving of 10 parts of glucose in 100 parts of physiologic saline solution intravenously will do much to combat dehydration and toxemia. A liter may be given two or three times in the 24 hours. This treatment will help also in preparing the patient for operation

In the case of lesions of the large bowel obstruction can often be made to subside under medical management. Nothing is given by mouth and the colon is washed out several times with warm physiologic saline solution. If it can possibly be done acute obstruction in the colon should be relieved in this way because then the patient can be gotten into a much better condition for operation. If however the pulse should become more and more rapid if vomiting should keep up if the temperature should rise and if the patient should show signs of prostration and failing strength operation should be done without further delay

Gastric lavage is sometimes helpful and in this way a physician can wash out material which has regurgitated from the bowel into the stomach. It makes the patient more comfortable and gets him into better shape for operation. It is probably well not to use solutions of sodium bicarbonate for this lavage because the patients are already suffering from an alkalosis due to the loss of gastric juice

The Treatment of the Paralytic Ileus that Follows Operations — This consists largely of the intravenous injection of a solution containing 10 grams of sodium chloride and 100 grams of glucose to the liter of water

Cathartics should be used as little as possible in the case of paralytic ileus because it is possible that they will still further paralyze the bowel. The use of morphin should also be avoided because in many persons it tends to reverse peristalsis and to increase the amount of vomiting. Barbital derivative given hypodermically may be helpful in relieving nervousness and anxiety in giving sleep and in allowing the body to fight a better battle

The induction of spinal anesthesia has been effective in overcoming the obstruction in a number of cases. It blocks inhibitory impulses that reach the bowel by way of the splanchnic nerves and it sometimes permits the resumption of peristalsis. Chemically pure acetylcholin, obtainable in ampules may also be tried in doses of from 200 to 400 milligrams dissolved in 300 c c of physio

logic saline solution Care should be used to introduce this solution very slowly into the veins Occasionally pituitrin seems to have a good influence, but at other times it only adds to the patient's discomfort The intravenous injection of a small amount of 25 per cent. sodium chlorid solution will sometimes start up peristalsis Eserin and atropin appear to be valueless, and they may do harm

The great problem that often faces the surgeon is shall he open the abdomen again or shall he not? If the obstruction should be a mechanical one and the surgeon should wait too long the patient will die but if the failure to pass gas is due to paralysis of the bowel another operation will not only be useless, but it may well take away what chance the patient has of life

In such a dilemma the active treatment of toxemia with intravenous injection of salt and glucose is particularly helpful because, as the patient improves, it may become evident that the bowels are not seriously obstructed, or else if they are obstructed the patient has been gotten into better shape to stand another operation

Subacute and Chronic Obstruction

The symptoms of obstruction will sometimes be present intermittently over a period of weeks and even months Although the disease may then be called chronic it is really made up of a number of episodes in which the symptoms are fairly acute This type of trouble is seen most frequently with strictures of the lumen of the bowel and with hernias either internal or external The history is often one of gradually increasing constipation associated with transient attacks of pain abdominal distention gurgling visible peristalsis and perhaps vomiting These attacks will last for several hours until the gas and intestinal contents again succeed in trickling through the obstruction This type of history is often obtained in cases of tumor of the small bowel

With obstruction of the colon about the hepatic or splenic flexure the colicky symptoms may closely resemble those of gall bladder disease The localization however will not be so typical and there are likely to be loud gurgling sounds associated with the pains

Intermittent attacks of obstruction are seen occasionally in patients who have had one or more abdominal operations One must not jump to the conclusion that obstruction is due to adhesions, because sometimes it is due to spastic contraction rings

If much weight has been lost it is well to ask if sufficient food has been eaten to maintain nourishment Not infrequently the patient either loses his appetite or else discovers that he is more comfortable when he eats very little Sometimes there are vague gastro intestinal symptoms such as flatulence and

soreness in the abdomen in between the attacks of obstruction In a few cases the patient has already discovered a mass somewhere in the abdomen

An occasional cause of chronic obstruction especially in older patients is impaction of feces possibly on the basis of diverticulitis of the colon For years constipation may get worse and worse until finally feces are not voided even with the help of purgatives and enemas The diagnosis usually can be made on rectal examination or when doughy masses are felt along the course of the descending colon After the bowel has been cleaned with repeated enemas the physician must always look with the sigmoidoscope and the roentgen ray to make sure that a carcinoma is not present In rare instances neglected fecal impaction can give rise to severe colitis or even peritonitis

The tremendous fecal impaction which is seen in cases of megacolon is peculiar in that symptoms of intestinal obstruction and back pressure are rarely seen and when present are likely to mean that some complication has developed, such as perforation of a stercoral ulcer

Occasionally the consultant will be called to see someone who is supposed to have chronic or subacute intestinal obstruction when the real difficulty is that the patient has a large colon which takes a week or ten days to fill A glance at the patient will show that he is not ill and a little questioning will reveal the fact that ever since childhood he has been able to let his bowels go for a week or two at a time without experiencing any discomfort

Treatment — The treatment in cases of chronic and subacute obstruction is not so urgent and anxious a matter as it is in the acute cases Often it is possible to tide a patient over the attack in which he is first seen and then every effort should be made to find the cause

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I W B W C A

Volvulus of the Sigmoid

Volvulus can occur at any one of the flexures of the colon, but it takes place most commonly in the sigmoid loop. The incidence varies in different countries; thus Alkonis and Muzeneed found it to be much more common in Russia than in Western Europe, and Wright stated that in some parts of Russia and Eastern Europe and Japan it is the cause of approximately a third of all cases of intestinal obstruction. It is fairly common in India but rare in England and America. The cause of this racial difference in susceptibility is not known, but it seems probable that differences in the length of the loop and of its mesentery and possibly in the nature of the food eaten have something to do with it.

The fact that this part of the bowel can be too long was shown by Fernstrom when after examining only fifteen sigmoid loops he found one that was approximately 2 meters in length. Ordinarily a loop 45 cm in length may be said to be long. Narrowness in the attachment of the mesentery of this part of the colon might well predispose to the formation of a volvulus. According to Fernstrom inflammatory disease around the large bowel, and particularly meso-sigmoiditis, can first give rise to an enlargement of the colon, and later this can predispose the patient to the formation of a volvulus.

Volvulus occurs most commonly among elderly people. In a group of 119 cases collected by Cifflhorn (quoted by Fernstrom) 40 of the patients were older than fifty one years and 94 were older than thirty years.

Rokitansky described three forms of volvulus: (1) that in which the rotation of the bowel takes place on its mesentery, (2) that in which the rotation of the bowel takes place on its longitudinal axis, and (3) that in which there is an intertwining of two coils. Fernstrom noted that the disease may go through three phases: (1) an acute one in which there are one or more sharp attacks, (2) a recurrent one in which at intervals there are attacks of short duration, and (3) a chronic one in which, almost daily, there are atypical, moderately severe or mild attacks of abdominal pain.

Pathology

During the development of a volvulus there is first hyperemia and edema and distention of the involved segment of the colon with the formation of a sulcus at the point of obstruction. This is followed by hemorrhagic exudation and later gangrene of the loop involved. In cases of recurrent or chronic volvulus there will be infiltration of the mucosa and submucosa with round cells, ulceration of the mucosa, hypertrophy of the muscular layers, and chronic lymphangitis and periphlebitis in the mesocolon.

Diagnosis

The diagnosis is often difficult and often missed The condition must be thought of in all cases in which it is obvious that there is something seriously wrong in the abdomen, and especially in the abdomen of a man or woman past middle age In acute cases the symptoms rapidly go from bad to worse and the patient soon is in profound shock A history of severe constipation and distress in the left lower quadrant of the abdomen may be elicited The first, fairly typical attack seen by the physician may be preceded by atypical pain which is persistent or intermittent over a long time Diarrhea may have alternated with constipation In a typical case by the time the severe and continuous pain appears flatus and fecal matter can no longer be passed By this time also abdominal distention and the usual signs of obstruction are likely to be present Rectal bleeding diarrhea and mucoid rectal discharge are sometimes seen

In our experience whenever some form of intestinal obstruction is suspected it is most helpful to have the roentgenologist make a film of the abdomen This so-called flat or scout plate is most helpful in that it shows the presence or absence of one or more loops of bowel distended with gas It may help to locate the obstruction in the small or large bowel and it may obviate the necessity of giving barium by mouth This is always to be feared in the presence of symptoms suggesting obstruction

The following report of a case illustrates the recurrent type of the disease A woman aged thirty years came complaining of repeated attacks of lower abdominal pain These attacks had been increasing gradually in severity for a year, and with them she could see waves traveling over the bowel The stools were small in caliber and she had great difficulty in passing them Occasionally there were flecks of blood in the stool The pain came two or three times a week It was very severe and was located in the lower left portion of the abdomen It was rhythmic and cramp like The attacks usually were relieved by hot applications or by the taking of a narcotic but in some of them the obstruction must have been almost complete The patient was advised by her physician to eat more bulky foods but as might have been expected this made her worse

The abdomen was tender to palpation below the navel and particularly in the left lower quadrant A roentgenogram showed a large redundant colon dilated from the cecum to the splenic flexures but without evidence of obstruction at this point The leukocyte count was within normal limits At operation 30 cm of a long redundant, sigmoid loop was resected and the patient was cured

Treatment

The treatment of the disease is generally surgical It is possible that in the recurrent and chronic types of the disease described by Fernstrom something might be accomplished by medical treatment, such as has been described by Hyman but even in these cases it is probably better to operate than to wait for a severe attack About all the physician can do is to give a low residue diet and keep the bowel clean with enemas

If in an acute attack the symptoms do not soon abate, a surgeon should be called As Nash has pointed out in acute cases a colostomy usually must be made at the time of resection of the gangrenous loop Deaver and Magoun advise that in some cases operation be done in two or three stages, and this precaution has often been taken with success by Sistrunk

For the intermittent type of volvulus such operations as ileosigmoidostomy, with anchoring of the flexures colopexy, plastic operations on the mesocolon and resection of the affected loop have been advocated by different surgeons For obvious reasons the mortality must be high

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Bloating and Pseudo Ileus

Many patients complain of flatulence and bloating, but on careful questioning it appears that their main trouble is really air swallowing and belching, and they never become actually bloated There is another small group of persons, made up almost entirely of neurotic women who present a striking clinical picture of bloating and pseudo ileus In them the abdomen is often hugely distended tense and tympanitic Peristaltic activity may or may not be visible. Aerophagia may be marked but it probably is not an essential part of the syndrome Constipation is always present and at times so marked that the patient is operated on In some cases there is no nausea or vomiting while in others vomiting becomes at times so severe that the material ejected has a fecal odor The patients suffer much discomfort, and sometimes complain of pain due to distention and pressure Rarely do they lose much, if any weight and except for their complaints and the striking appearance of the abdomen they

seem to be in good health Most of them when first seen by a consultant have already submitted to one or more operations for relief of intestinal obstruction' The two following reports of cases will serve to illustrate the clinical picture as it is usually presented

A woman, aged eighteen years came complaining of symptoms which at first were thought to be due to intestinal obstruction She had entered a convent at the age of fifteen years When she was sixteen he was confined to her bed with an acute illness with high fever and chills severe constipation and pain in the left lower quadrant of the abdomen She recovered from the acute attack and was left with the constipation This became more and more intractable until an appendectomy was performed Two months later the constipation was so severe that she returned to the hospital in her home town During the next two months physicians made every effort to relieve the constipation A hemorrhoidectomy was performed and following this there appeared the abdominal distention which was so evident when she came to the Mayo Clinic

Although the patient was well nourished and judging by her appearance, was not seriously ill she came in an ambulance with the abdomen distended to a size larger than that characteristic of a nine months pregnancy There were two distinct regions of distention separated by a furrow located slightly orad to the navel It looked as if the stomach were above the line and the intestines below

A large mass of feces was found impacted in the sigmoid flexure and rectum, but its removal did not relieve the distention Fecal matter was vomited every day for a week Chemical and cytologic examination of the blood and urine did not show anything abnormal

Feeding by mouth was discontinued and fluids were given intravenously The intestine was irrigated twice daily until the return were clear Finally spinal anesthesia was induced and complete reduction of the abdominal distention resulted Unfortunately the swelling returned as soon as the anesthesia wore off Four days later the abdomen was opened and all the viscera were examined but nothing abnormal could be found The patient was completely relieved of the distention for two weeks until the day when she discovered that nothing curative had been done at the time of operation then the trouble returned She was dismissed forty days after the exploration somewhat improved but still having great difficulty in controlling constipation

A woman aged twenty two years had been constipated for six days and had vomited the evening before and again the morning of examination She continued at her work as a maid in a hospital until an hour before examination That morning she had taken salts then castor oil and finally soap suds enemas but had failed to secure fecal material Two years before this attack during an appendectomy a piece of wire had been removed from the last coil of the ileum

Following this operation she had had several attacks of severe constipation. They lasted several days and returned every two or three weeks

The patient was well nourished The abdomen was distended to the size seen usually with a seven months pregnancy Pelvic examination revealed nothing unusual Rest in bed the application of hot abdominal stupes and the giving of irrigations of hot saline solution brought but little relief Exploration revealed extensive adhesions around the terminal coil of ileum with distention of the bowel above The adhesions were freed the patient was relieved, and except for minor attacks similar to the one she had had prior to this operation, she got along well for a year Then the abdominal distention reappeared, and there was so much difficulty in emptying the bowel that she was operated on again and the presacral nerves were sectioned This gave so little relief that she had to be operated on again At this time gallstones were found and the gallbladder was removed Marked improvement followed this operation It is hard to believe that the whole clinical picture could have been produced by a diseased gall bladder but during the six months in which she was under observation after its removal she continued to improve

In most of our other cases repeated operations have failed to show any causative lesion, and the impression remains that the cause of the disease is nervous or hysterical in nature In favor of this view is the fact that in most of the cases the patient was a neurotic woman The condition suggests an inherent or acquired inadequate mechanism of elimination of some of the intestinal gases Strange to say however in some of these bloated patients abnormal amounts of intestinal gas cannot be demonstrated with the fluoroscope or in the roentgenogram Whether the state is entirely neurogenic or whether it is due to failure of absorption or both cannot be said at this time In some of these cases, at the time of exploration C H Mayo has noted a peculiar, possibly edematous swelling of the intestinal wall

Treatment

One of the most important preliminaries in the treatment of these patients is the obtaining of their confidence and cooperation Before medical treatment is begun, every effort must be made to find or rule out organic intestinal obstruction Efforts can be made then to clear out the bowel This may be accomplished with the help of enemas laxatives and a low residue diet Since many of these patients swallow much air as they drink liquids, it sometimes helps to put them on a rather dry diet

If there is much belching the patient must be taught to break herself of the habit If roentgen ray examination shows that the stomach does fill with air, it will help greatly to have the patient pass a small Sawyer tube after each meal

so as to remove the gas Gas trapped in the splenic flexure can sometimes be moved into the rectum by having the patient hang over the side of the bed especially after taking a small enema Sedatives and soporifics may be helpful In some cases the distention will disappear in a few minutes after the giving of a hypodermic injection of morphine or codein Occasionally a dose of surgical pituitrin will be helpful In every case it would probably be well to place the patient on an elimination diet or to starve her for a few days to see if any particular foods are responsible for the condition Abdominal exploration may become necessary, but should be postponed as long as possible

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Duodenal Stasis

There are cases in which the duodenum has difficulty in emptying itself and as a result the patient suffers with a number of symptoms such as nausea dizziness headache a feeling of fulness and perhaps a sense of auto-intoxication

The commonest cause for this condition is supposed to be a constriction of the distal end of the duodenum by the vessels in the root of the mesentery and theoretically relief should be obtained from the operation of duodeno-jejunostomy

Although there is no doubt that the roentgenologist occasionally sees duodenal dilatation and stasis and although one would expect troublesome symptoms to arise from such stasis the point to be emphasized is that the surgeon had better not try to correct the condition until after repeated examinations the roentgenologist can assure him that it is fairly constant Too often it is a transient phenomenon and at operation a cause for it cannot be found Some surgeons who at first were enthusiastic over a few apparently cured patients later discovered that the symptoms tended to return in spite of the maintenance of good duodenal drainage

It seems obvious, then that although duodenal stagnation is occasionally observed its relation to the symptoms complained of by the patient is always problematic and surgical relief of the condition should not be attempted until the case has received much study by some gastro-enterologist who has a wide experience and good clinical judgment

W C A

Carcinoma of the Colon and Rectum

It is an unfortunate fact that the medical profession is still not making the diagnosis of carcinoma of the rectum and colon early enough In many cases physicians do not recognize the disease even when it is in its terminal stages Part of the blame for the late arrival of the patients in the surgeon s consulting room must be laid at the door of the layman, who is often loath to discuss, even with his physician matters that have to do with defecation and rectal discharges Unfortunately also, the layman has not yet been educated to the point where he realizes the danger that can lurk behind a little rectal bleeding or an attack of mild obstruction Still worse the physician also fails often to recognize the dangerous import of these symptoms, and instead of inspecting the anus or passing a finger into the rectum, he spends precious weeks or months on treatments for hemorrhoids , or colitis ', or 'dysentery"

In a large percentage of the cases of carcinoma of the rectum seen every year at the Mayo Clinic the patient gives a history of having recently been treated elsewhere for hemorrhoids Sometimes he or she comes with a sheaf of 'negative roentgenograms recently made of stomach and gallbladder and even colon It is saddening to think that if only a rectal examination had been made with the finger the diagnosis would have been easy

Pathology

Among the malignant lesions of the colon and rectum are epitheliomas, adenocarcinomas colloid carcinomas polypoid carcinomas scirrhous annular carcinomas and lymphosarcomas As is pointed out in the section on polypo s, carcinomas of the colon commonly originate in polyps The growth may be single or multiple and it is not uncommon to see several, apparently unrelated, carcinomas in the one colon

Some of the difficulties encountered by the clinician in localizing lesions in the colon may be due to the fact that the sensory nerves supplying the right half leave the abdomen by way of the solar ganglia, while the left half is supplied by nerves which go out to the cord by way of the sacral plexus Possibly for this reason the pain produced by tumors of the colon is not always referred to that part of the abdomen which overlies the lesion Another reason for this confusion may be found in the fact that, when an obstructing carcinoma is present in the left half of the colon most of the distention of the bowel is likely to be found in the thin walled right half Under these circumstances it is not surprising that the pain may be felt largely on the right side of the abdomen

Symptomatology

In studying the symptoms produced by disease of the colon it would probably be helpful to take up first the lesions in the right half and later those in the left half

Lesions of the Right Half of the Colon —The symptoms produced by lesions in the right half of the colon may be first those of anemia second, those of indigestion and back pressure and third various more or less accidental complications In the cases of many of the cancers of the cecum the first and most striking symptom and often the only one, is a secondary type of anemia This may reach extreme grades

As W J Mayo long ago pointed out and as Alvarez Judd MacCarty and Zimmerman showed later with carefully gathered figures, the tendency to produce anemia is progressively less marked with cancers of the transverse the descending and the pelvic portions of the colon The cause for this gradation seems to be a gradation in the surface area of the tumors from an average of approximately 52 sq cm in the cecum to 29 sq cm in the rectum This gradation is dependent again on a gradation in the diameter of the colon which varies from about 6 cm in the cecum to 2 5 cm in the sigmoid The patient seeks relief when the lumen of the bowel becomes more or less blocked, in the descending colon this can happen when the tumor has grown to the size of a walnut in the cecum it does not happen until the mass is as large as the palm of a man s hand

The essential factor in the production of anemia by cecal carcinomas seems to be the presence of a large ulcerated area from which blood can ooze and through which bacteria can enter Nowhere else on the inside of the body except possibly in the fundus of the stomach can ulcerating cancers be found so large as in the cecum and nowhere else are such extensive raw surfaces in contact with such a concentrated culture of organisms many of them virulent and when injected into animals capable of producing severe anemia

It is for this reason that whenever a patient presents himself with marked secondary anemia and few symptoms to point to the source of the trouble it is well to look first at the cecum and then at the fundus of the stomach

When pain or more commonly distress is produced by cancers of the right half of the colon it is usually referred to the epigastrium probably because the sensory nerves involved go out by way of the solar plexus and the splanchnic nerves It must never be forgotten that epigastric distress can be due just as well to disease of the right half of the colon as to disease of the stomach

The distress which is produced by cancer of the cecum is usually not of the type found in most cases of peptic ulcer but at times it can simulate it Ordinarily it is more a feeling of hyperperistaltis or intestinal unrest It may be a

cramp like feeling or an ache Rarely, the symptoms will suggest the presence of obstruction The usual lack of symptoms of obstruction with lesions of the cecum is due probably to the fact that in this part of the bowel the lumen is large and the contents are so liquid that they can slip past the growth Furthermore cancers in the cecum show little tendency to encircle the bowel and to obstruct it they are more likely to grow through into the surrounding tissues or to produce perforation Mild indigestion simulating that of chronic appendicitis is common especially if the lesion involves the ileocecal sphincter or is near it

Not infrequently growths in the right half of the colon become large enough to be felt by the patient before they produce any symptoms Occasionally also loss of weight and strength will be the first symptoms complained of In most cases the anemia cannot be ascribed to the passage of large amounts of blood by rectum because the patient has not noticed any

Some observers have suspected that the anemia which is so pronounced with carcinoma of the cecum might be due to the loss of some important function of the mucous membrane which the body cannot spare, but this does not seem probable because when tuberculosis almost destroys the cecum it ordinarily does not produce marked anemia and when the cecum is short circuited for a carcinoma and left for six months or a year, the patient s blood may come back almost to normal Furthermore if the mucous membrane of the cecum were in any way essential to life and health the fact would long since have been discovered when surgeons resected this part of the bowel

Alternating constipation and diarrhea are symptoms sometimes associated with disease in the right half of the colon The diarrhea is rarely, if ever, severe the stools may be loose and watery and they may contain considerable mucus Only rarely do they contain visible blood

Lesions of the Left Half of the Colon — When a carcinoma grows in the left half of the colon it produces a clinical picture quite different from that seen when the tumor is in the right half The colon on the left side is narrower, the fecal material is dryer and more or less formed and its progress to the rectum is much more easily stopped by a growing obstruction For this reason patients with neoplasms in the left half of the colon are driven to seek the help of a physician in the earlier stages of the disease when the symptoms are those of obstruction Unlike the patients with carcinoma of the cecum, they cannot put off going to the doctor until they are markedly anemic and weak

Unfortunately there need be no symptoms in the earliest stages of the growth of an intestinal cancer because the neoplastic cells do not seem to irritate either the muscle or the mucous membrane, and as a result there is neither spasm nor discomfort nor diarrhea Furthermore so long as the tumor is polypoid and not ulcerated, there is no bleeding and no tendency to hemorrhage

While the tumor is growing, there may be periods in which the symptoms will be those of partial obstruction with abdominal cramps gurgling flatulence bloating and a frequent desire to go to stool Sometimes there is considerable diarrhea Occasionally a mass may be felt fairly early in the course of the disease This may represent not only the tumor but a mass of feces collected above it

The colloid type of carcinoma is likely to produce more obstruction than does the *adenocarcinoma* It is more likely to ulcerate early and to grow through the wall of the colon into surrounding tissues

Tenesmus is characteristic of lesions low in the rectum and of those which involve the anal sphincter When tenesmus is associated with lesions in the recto-sigmoid region of the bowel it suggests the presence of infiltration with cancer cells of all parts of the wall of the bowel

Sarcoma — Sarcomas and lympho-sarcomas give no special symptoms which will enable the clinician to distinguish them from carcinomas A tentative diagnosis can be made, sometimes when it s found that the lesion is in the perirectal tissues In such cases the mucosa may not ulcerate until late in the course of the disease Digital examination may give the impression that velvety excrescences are narrowing the lumen of the bowel

Intestinal Obstruction – The scirrhous type of carcinoma which tends to grow as a dense ring around the bowel often produces characteristic symptoms It tends to grow outward away from the lumen and into the intestinal muscle It produces the so-called napkin ring contraction which shows so clearly in roentgenograms Not infrequently the first sign of the presence of such a lesion is an attack of obstruction in which the passage through the bowel becomes entirely blocked In other cases there may be several short attacks of obstruction in which relief is obtained by the giving of enemas or purgatives

Peristalsis can seldom be seen in the obstructed colon unless the patient is *very thin* Then it may be noted that the waves are much slower than those ordinarily seen in the obstructed small bowel they are sluggish and the muscle is slow to relax

A remarkable feature of obstruction in the colon especially when it comes on slowly is the patient s ability to tolerate it With many colonic cancers the history will show that obstruction has developed gradually during a period of weeks or months As a result the patient seems to get used to it and when the block becomes complete the bowel will for several weeks tolerate it remarkably well We have seen patients who except for abdominal distention were perfectly comfortable for weeks after complete obstruction formed in the left half of the colon

In the later stages of partial obstruction due to tumors in the recto-sigmoid portion of the bowel the main symtpom may be diarrhea Apparently the

fecal material liquifies above the obstruction and is then able to come away through the narrow lumen

Diagnosis

The value of the examining finger and the proctoscope in the diagnosis of intestinal disease cannot be over rated Fortunately most carcinomas of the rectum and recto-sigmoid can be reached by the finger In some cases the other hand must be used on the abdomen to push the lesion down within reach of the exploring finger With the proctoscope the examiner can see the lesion, and if he desires, he can secure material for histologic examination The examination of the specimen thus removed will give information as to the type of the growth and also as to the degree of its malignancy Not infrequently the knowledge that a growth appears to have a high degree of malignancy will help the surgeon in deciding whether or not it would pay to go ahead with attempts at radical removal Follow up studies indicate that the method used by Broders has definite prognostic value The fact that the biopsy shows undoubted cancer may be of great help also to the physician when it comes to convincing the patient and his relatives that an extensive serious, and often repugnant operation is necessary

With lesions of the rectosigmoid junction it is important to localize the growth accurately because the surgical approaches to the rectum and the sigmoid are different Not infrequently a lesion which is situated in a long, redundant sigmoid flexure will through some telescoping of the intestinal wall, move down into the rectum The fact that it has slipped down can usually be determined with the help of the finger and rarely in any other way Ordinarily, a lesion which is beyond the reach of the index finger is above the point of the peritoneal reflexion and thus in the sigmoid portion of the large bowel With the help of the finger much can be learned also about the type, size and degree of fixation of the growth and thus about its operability or inoperability

Next to a good history and a good examination of the rectum with the finger and sigmoidoscope the most important help in diagnosing diseases of the large intestine comes from a careful roentgenologic examination As has already been pointed out in this chapter an opaque meal should never be given by mouth whenever there is the least reason to suspect that there is an obstructing lesion in the colon The impaction of the barium above the growth may bring on symptoms of acute obstruction and this may lead to the death of the patient It is much safer to inject barium from below, watching to see how the bowel fills The deformity produced by the different types of malignant lesions is often so characteristic that the diagnosis can be made by the roentgenologist alone (Fig 4)

When the existence of a malignant lesion of the large intestine has been determined, it is of great importance to look for metastases There are a few



Fig 4 Roentgenogram after a barium enema on a patient with cancer of descending colon

cases on record in which a large Virchow s node has been found in the supra clavicular fossa A roentgenologic examination of the thorax should always be made The liver should be palpated carefully and its size and contour should

be noted in the roentgenogram of the abdomen In view of the fact that the liver is the commonest site of metastasis from colonic carcinomas, it is well sometimes to test the function of this organ The finding of a high degree of dye retention generally means that the liver contains cancer cells With epitheliomas of the anus and with low lying rectal carcinomas the lymph nodes of the groin should always be examined

Differential Diagnosis

When the evidence points to the presence of a malignant tumor in the large bowel there remains the task of excluding other diseases One of the first things to be thought of is a polyp Since there is always the possibility that a polyp is cancerous or that it will become so attempts at differential diagnosis are not of much value The essential thing is to get the lesion out, and then the pathologist can say how benign or malignant it is

Particularly when dealing with a lesion in the cecum, the clinician must think of tuberculosis and especially of the hyperplastic form Ordinarily tuberculosis appears in young people while carcinoma appears usually in persons past middle age The anemia which is so characteristic in cases of carcinoma, usually is absent with tuberculosis and the patient may be in good flesh It must be remembered of course that many patients with carcinoma of the colon appear to be perfectly well It is helpful to find signs of active or healed tuberculosis elsewhere in the body and particularly in the lungs Not infrequently surgical exploration of the abdomen is necessary to make certain of the diagnosis

Diverticulitis in the left half of the colon, with the formation of small abscesses and a large mass sometimes presents serious diagnostic difficulties even after the surgeon has opened the abdomen The most important point is that in the roentgenogram the segment involved with diverticulitis is generally longer than it is in carcinoma and the margins of the constricted part are more tapering and less abrupt The roentgenogram will probably show also that there are diverticula either in the narrowed region or in other parts of the bowel

Fecal impaction in the rectosigmoid region will occasionally produce a nodular tumor which can be removed with the help of enemas and purgatives Rectal strictures of inflammatory and traumatic origin must be distinguished from those due to scirrhous carcinoma Perirectal lesions such as lymphomas and occasionally the induration which results from an inexpert injection of hemorrhoids may cause confusion in the mind of the examining physician Amebic dysentery can usually be recognized by the presence of mucosal ulcers in the rectum and by the discovery of Endameba histolytica in the stool It must

never be forgotten however that the presence of amebic cysts in the stools does not rule out the presence of a carcinoma in the bowel Chronic ulcerative colitis can usually be recognized by its typical proctoscopic and roentgenologic picture

Treatment

The treatment of carcinoma of the colon and rectum must of course be surgical in nature It is advisable however that the physician cooperate at all times with the surgeon not only in the preparation of the patient for operation but also in the post operative care

As everyone knows the mortality attendant on operations on the colon has always been high and much of it has been due to peritonitis Resection of part of the colon is particularly dangerous first because this segment of bowel contains a highly infectious material second because when ulceration of any kind is present in the mucous membrane paths are opened up through which bacteria can pass out readily into the lymph channel of the mesentery and as a result the operator must work in an infected field third because the blood supply is not so rich as it is in the small bowel and greater operative skill is needed if necrosis of tissue and subsequent leaking at suture lines is to be avoided Finally it must be remembered that many of the patients with cancer are old, many have been weakened by suffering and many are in poor shape for any type of operation

There are a number of other anatomic and physiologic peculiarities that conduce to the high mortality seen commonly with operations on the colon One is the thinness of the muscular wall of the colon as compared with that of the small bowel furthermore in older people the important tunica propria which contains lymph channels and blood vessel frequently is replaced by fat. The peristaltic contractions of the colon which normally are greater in depth and more powerful than those in the small bowel are bound to put great strain on suture lines and as a frequent result there is leakage and the formation of abscesses and patches of peritonitis

It seems probable also that as feces accumulate behind a slowly growing obstruction, the mucous membrane of the bowel becomes less and less able to block the passage of bacteria into the lymph channels of the mesentery If in addition the surface of the growth is fungating and ulcerated the paths of infection are even more widely opened In patients with such a lesion several types of bacteria usually can be grown from lymph nodes removed at a considerable distance from the tumor

It is largely on account of this leakage of infection that it is so dangerous to operate on patients at a time when the bowel is obstructed The

be noted in the roentgenogram of the abdomen In view of the fact that the liver is the commonest site of metastasis from colonic carcinomas, it is well sometimes to test the function of this organ The finding of a high degree of dye retention generally means that the liver contains cancer cells With epitheliomas of the anus and with low lying rectal carcinomas the lymph nodes of the groin should always be examined

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40 per cent cream 1 egg 160 gm of candy 4 arrowroot wafers and 800 c c of fruit juices containing 160 gm of cane sugar A typical menu is given in the following table

TABLE 1

Breakfast
- 1 glass o per cent fruit juice
- 40 per cent. cream 25 gm
- 1 egg
- 1 square of butter 10 gm
- Coffee *
- Arrowroot wafers

9 A M
- Candy 160 gm

Dinner
- Lean beef 1 o gm
- *Broth with 1 square of butter weighing 10 gm*
- Gelatine 100 gm, or 2 heaping tablespoonfuls
- 40 per cent cream 50 gm
- 1 glass 20 per cent fruit juice
- Tea or coffee
- Arrowroot wafers

3 P M
- 1 glass 20 per cent fruit juice

Supper
- Broth with 1 square of butter weighing 10 gm
- Steamed rice 100 gm or heaping tablespoonfuls *
- 40 per cent cream 75 gm
- 1 glass 20 per cent fruit juice
- Tea or coffee
- Arrowroot wafers

* Sugar as desired.

A mild laxative such as fluid extract of senna is usually given every twelve hours in doses of from 2 to 8 c c (30 to 120 minims) and the bowel is washed out twice a day with enemas of warm physiologic saline solution This cleansing process is kept up until 24 hours before operation

After the bowel has been thoroughly emptied in this way, the next step is to quiet the peristaltic movements as much as possible This is accomplished with the help of small doses of some sedative such as camphorated tincture of opium Usually when the operation is scheduled for the early morning 2 c.c (30 minims) is given at P M the day before and 4 c c (1 dram) at 6 P M and the same dose again at 10 P M

Types of Operation — Most of the malignant lesions of the colon are best

risk can be much lowered if the physician will first overcome the obstruction by a suitable cleansing of the bowel and then if, with the help of rest, forced fluids and a low residue diet he will get the patient into a better physical condition

It has long been noted by surgeons that when the patient has survived a colostomy or other simple abdominal operation, done with the idea of preparing the way for resection of an obstructing lesion, he is likely to stand the following big operation better than he stood the first smaller one This peculiar behavior has long been explained as being due to the fact that at the first operation some peritoneal soiling took place, in a way the peritoneum was vaccinated, and this served to raise its resistance to subsequent infection With these observations in mind a number of workers in the past have tried, in animals, to immunize the peritoneum by injecting dead and living bacteria They had some success, and later v Mikulicz tried the same experiment on men and women with vaccine made of killed colon bacilli Unfortunately the reactions he obtained were so severe that the procedure was given up

A few years ago at the Mayo Clinic Hermann obtained such striking results in the way of protecting dogs from peritonitis that Rankin and Bargen were encouraged to try the experiment again in men and women about to undergo an operation on the colon As antigen they used killed colon bacilli and green producing streptococci grown from strains obtained from the peritoneal cavity of patients who had died of peritonitis Although after the injection the patients have a rather severe and painful reaction with a very tender abdomen, some fever, and often a chill they are always well again in twelve hours

The vaccinations are now made as follows after first injecting enough procain so as to produce a small area of anesthesia in the skin and superficial tissues, a dulled spinal puncture needle is thrust through the abdominal wall at a point as far as possible away from the site of the malignant growth Through this needle is injected 10 c c of physiologic saline solution with usually 0 5 to 1 c c of a suspension containing from 0 5 to 1 billion killed organisms This is done seventy two hours before any colonic operation is to be performed The results have been excellent and during the last three years peritonitis has been materially reduced as a cause of death after colonic operations

The next most important peroperative procedure is the so called decompression of the obstructed bowel above the growth In order to keep from adding to the mass of feces already stagnating above the growth the physician keeps the patient for from three to six days on a diet containing just as little residue as possible Rich broths tea and coffee are allowed in unrestricted amounts In addition there is given each day a small amount of lean beef 100 gm of steamed rice 30 gm of butter 100 gm of plain gelatine 150 c c. of

When the bowels tend to be constipated this covering is sufficient to control the situation, and the patient will be able to go about his or her business and live like a normal human being When there is a tendency toward loose stools constantly or in spells the simplest type of bag should be used Naturally when the stools are loose it will be helpful if the patient will adhere to the low residue diet which is prescribed in cases of diarrhea It may be helpful also to eat only twice a day and to avoid fluids It must be remembered that every time the patient eats or drinks a series of peristaltic waves is sent off down the bowel It would probably be hurtful also to chew gum as swallowing starts up intestinal activity

Ordinarily we prescribe the following diet for patients with a colostomy and tell them to regulate the bulk and softness of the stool by increasing or decreasing the amount of fruit lettuce fat milk and yeast

DIET FOR PATIENT WHO HAS UNDERGONE COLOSTOMY

Breakfast	*Dinner*	*Supper*
Orange juice ½ glass	Meat 1 serving	Cheese 1 serving
Bacon or egg 1 serving	Potato 1 serving	Meat 1 serving or 2 eggs
Toast as desired	Shredded lettuce 1 serving	Potato or substitute
Butter as desired	Bland dessert no fruit	Fruit ripe banana or other bland fruit
	Bread toast or crackers as desired	Bread crackers or zwiebach as desired
Coffee if desired	Butter as desired	Butter as desired
	Jelly if desired	Jelly if desired
	Milk (boiled) 1 glass	Milk (boiled) 1 glass
	Tea if desired	Brewers yeast
	Brewers yeast	

Radiotherapy — In recent years radium has been used not only as a palliative measure in the case of patients with inoperable lesions but also in some cases in which it was depended on to work the cure In a few cases it has been used as a preliminary to operation with the idea of causing shrinkage in the size of the lesion and reduction in the danger of infection Unfortunately the group of rectal carcinomas in which it seems worthwhile to try radium is but a small one In a few cases, deep roentgen ray therapy may be tried

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treated by two stage operations. Thus the best operation for carcinoma of the rectum generally is colostomy and posterior resection. The type of colostomy must depend upon the location of the lesion and the experience of the surgeon. For a lesion at the recto sigmoid junction it is usually best to make a 'single barrel' colostomy preparatory to removal of the tumor. When the lesion is below the recto sigmoid junction and a posterior resection must be done a double barreled colostomy is satisfactory. Mobile lesions in the left half of the colon from the middle of the transverse portion to the recto-sigmoid junction, can be removed satisfactorily by the Mikulicz operation or some modification of it.

Rankin has shown that his 'obstructive resection' with clamps has definite advantages over the original Mikulicz type of procedure. It has the good features of the Mikulicz operation and in addition, it has the advantage that much of mesentery can be removed so that there is less danger of a return of the cancer. Moreover because the tumor is removed at the time of the first operation and not left for several days in contact with the wound, there is less danger of a recurrence of carcinoma in the abdominal wall.

Rankin's operation can be done only in those cases in which the colon above the lesion has been completely emptied beforehand, because when the clamp is used the bowel is left obstructed for from forty eight to ninety six hours. At the end of this time when the abdominal wound has become well sealed, the clamp on the orad end of the colon is released and later the stoma is closed as in a typical Mikulicz operation.

For lesions of the cecum and ascending colon, the best operation is ileocolostomy with subsequent resection of the colon orad to the stoma. In a few cases these procedures can be performed in one stage but usually the risk is reduced by dividing the work.

Good postoperative care is important. Even liquids should not be given by mouth until the patient begins to pass gas. During this time the level of the body fluids should be maintained by the giving of solutions of glucose intravenously and sodium chloride subcutaneously. The giving of sedatives intravenously is often of considerable help. As soon as the patient is able to eat, every effort should be made to build up his or her resistance.

The Care of a Colostomy — The care of the artificial anus which has to be made preparatory to the removal of lesions below the recto-sigmoid juncture is an art in which the patient must be instructed. Success in handling the situation will result in a satisfied patient while failure will mean misery. Experience with hundreds of patients with an artificial anus has taught us that the simpler the apparatus used for the control of the opening the better. The best one found so far is a piece of oilcloth covering a pad of tissue paper or cotton. This is held in place by an elastic belt of special design.

uted throughout the colon (Fig 5) Their numbers usually will be found to decrease as one passes from the left to the right side of the bowel In a group of persons with diverticula demonstrated at necropsy the pouches were limited to the sigmoid loop in 29 per cent they were found in all parts of the colon in 68 per cent and in 3 per cent they were found everywhere except in the sigmoid flexure

According to Mailer the diverticula appear first as little pits in the mucosa and submucosa they then extend through the circular muscle and on to the longitudinal muscle As it grows the diverticulum either breaks through the muscle or carries some of this tissue ahead of it When the longitudinal muscle remains on the diverticulum it eventually atrophies perhaps on account of the stretching Mailer was not able to find any signs to indicate that inflammation ever precedes the formation of the diverticula Most of the pouches have little if any muscular lining and therefore nothing to help empty them when they become filled with fece

Mailer says The exact situation of diverticula in relation to the circumference of the bowel is remarkably constant They appear between the mesocolic and the antimesenteric longitudinal muscle bands rather closer to the latter than to the former The position of the diverticula is definitely related to the points where the blood vessels enter the bowel from the mesentery

Why and how do these pouches form and why do they wait until middle or old age before they appear? So far no one knows exactly but it may be surmised that like hernias elsewhere in the body they come when age with its attendant wear and tear and atrophy of tissues has thinned the muscle fibers and separated them Many writers believe that increased intra-colonic pressure is a cause but as yet no theory is backed by a sufficient number of observations to make it entirely satisfactory If constipation were a cause one would expect to find the condition more common in women than in men but the reverse is true Spriggs and Marxer believed that with the roentgen ray they could recognize the pre-diverticular state in which there is a regional weakening of the colonic muscle It may be significant that most of the persons with diverticulosis are overweight

One of the important things for the physician to remember is that in a particular patient the discovery of a diverticulosis even of striking degree and extent need not explain the symptoms complained of he must not cease therefore in his efforts to make a real diagnosis because if he does he may overlook the far more important gallstone duodenal ulcer or gastric cancer that is really responsible for all of the trouble

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Diverticulosis and Diverticulitis of the Colon

Diverticulosis of the colon is a condition in which there are one or more little pouches projecting from the wall of the bowels From studies made with the roentgen ray and at necropsy it has been estimated at the Mayo Clinic that perhaps 5 per cent of persons more than forty years of age have colonic diverticula According to Mailer s calculations in persons older than forty five years one in eight shows this abnormality In only 31 out of 592 cases studied by Rankin and Brown was the age less than forty

In only 17 per cent of 592 cases of diverticulosis was there evidence of diverticulitis or inflammation arising in the pouches In their series of 1 000 cases Spriggs and Marxer found 10 per cent with diverticulosis and 5 per cent of these with signs of diverticulitis In the 100 cases of diverticulosis there were 71 men to 29 women

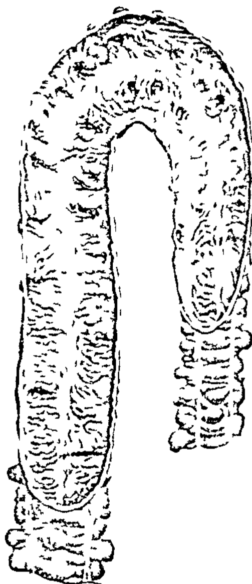


Fig 5 Diverticulosis of descending colon from male subject aged 72 (H H Maxwell Telling Courtesy of British Journal of Surgery)

Diverticulosis

The pouches are found most commonly along the sigmoid flexure, but they may be distrib

come on so suddenly and will be so complete that the physician will fear the presence of carcinoma In such cases he will be greatly helped if he can elicit a history of a number of similar attacks in years past The long duration of the disease will not rule out the presence of carcinoma but it will add weight to the diagnosis of diverticulitis

Diarrhea will be observed in a few of the cases It is seldom a true diarrhea but more a tenesmus associated with the passage of mucus or pus or perhaps a little blood Occasionally when a small abscess ruptures into the bowel, pure pus will be passed Red blood will be seen in the stools in perhaps 2 per cent of the cases

On examining the patient, the physician will often find a tender easily palpable sigmoid flexure and in many of the cases a definite mass will be made out Not infrequently there will be a little fever and perhaps some chills Occasionally some of the diverticula will be low enough so that their mouths can be seen through the sigmoidoscope but ordinarily the usefulness of the sigmoidoscopic examination lies largely in the fact that it serves to rule out the presence of carcinoma in the lower part of the bowel Examination of the bladder will sometimes reveal an inflamed area or the mouth of a fistulous tract and perhaps some gas and feces Occasionally roentgen ray examination of the patient standing will show a bubble of gas in the urinary bladder

Diagnosis — The diagnosis usually is made with the help of the roentgenologist but diverticulitis must always be thought of when a stout man or woman, past middle age complains of recurrent attacks of pain and discomfort in the lower part of the abdomen and especially on the left side The physician will think particularly of this disease when these attacks of pain are associated with mild obstruction of the bowel and a little fever and when they have recurred for several years without causing the patient to lose in weight and strength Usually a doughy mass can be felt and often it will be learned that in previous attacks a tumor formed and later disappeared

As has been mentioned in other places in this chapter whenever the clinician has reason to fear the presence of a carcinoma or any other obstructing lesion in the colon he should avoid the giving of barium by mouth it is likely to become impacted above the obstruction so that later the surgeon will have much difficulty in removing it It is safer to use the opaque enema and to watch it carefully as it runs in

The roentgenologist will be inclined to make the diagnosis of diverticulitis when he finds a segment of colon in which there are diverticula and in which the bowel is contracted and highly irritable The outlines of the colonic wall in the narrowed segment usually will be smoother than they are in the case of carcinoma the zone of obstruction will be wider and on each side of it there will be some tapering of the lumen of the bowel With carcinoma the shoul

Diverticulitis

When diverticula become inflamed the resulting lesions are those of diverticulitis The disease may be acute or chronic and recurrent and it may be complicated by the formation of fistulas and abscesses The fistulas may burrow to the outer surface of the body, or they may involve some other part of the bowel or the urinary bladder

Symptoms — According to Mailer the symptoms in order of frequency are pain in the left iliac fossa urinary disturbances pain in both lower quadrants of the abdomen increasing constipation poorly localized abdominal pain, epigastric distress pain in the rectum, bleeding from the bowel, and diarrhea The stories can be divided into six types In type 1 there is a long history of gradually increasing intestinal distress ending in symptoms of acute obstruction In type 2 there is a history of repeated attacks of obstruction with intervening periods of good health In type 3 there is a combination of the symptoms seen with the first two types in other words, there is a gradually increasing constipation punctuated by attacks of obstruction In type 4 the symptoms are those of bladder trouble In 14 out of 100 cases studied, a vesico-sigmoidal fistula could be demonstrated In type 5 cancer is associated with the diverticulitis and in type 6 the symptoms are unusual and hard to interpret

Abdominal pain is the commonest symptom It may be intermittent and sharp or it may be a dull aching discomfort which is more or less persistent The pain usually is felt in the region of the descending colon and sigmoid flexure, but it may be anywhere and even in the right lower quadrant of the abdomen

The direction in which the pain is referred will depend largely on the presence or absence of complications and particularly on the way in which the infection in the colon spreads to neighboring organs For instance, if an inflamed diverticulum becomes attached to the bladder, the symptoms are likely to be largely those of vesical irritation According to Mailer, adhesions had formed about the colon in 74 of 100 cases of diverticulitis studied The bladder was involved 24 times the left wall of the pelvis o times and the small intestine 12 times

Often it is helpful to find on questioning the patient that there have been other attacks of pain in the past, associated, perhaps with severe constipation In these spells there may have been fever and perhaps chills Constipation is complained of in perhaps 50 or 60 per cent of the cases Obviously, unless this symptom has been very trying its presence cannot be of much help in making the diagnosis, because it is met with so commonly in persons who do not have diverticula

In 9 or 10 per cent of the cases of diverticulitis, intestinal obstruction will

it appears that they are not particularly subject to malignant disease of the bowel The transition that at times takes place has been well described by Wilson

Treatment — Diverticulitis should be treated medically in all but those few cases in which serious complications occur Occasionally as perhaps when there is a tumor associated with a good deal of obstruction and diagnosis is difficult it may be safer to open the abdomen than to wait One difficulty with operating is that, ordinarily a fairly long segment of the bowel is affected by the disease and in order to remove it all the surgeon would have to resect widely For this reason when the surgeon is forced to operate he must often make a colostomy instead of attempting a resection In the presence of an infected field and adhesions to surrounding loops of bowel or to other viscera the risk of resection is so large and the mortality so high that every effort should be made to spare the patient the dangers attendant on it

In acute cases treatment consists of rest in bed with a low residue diet and colonic irrigations with warm physiologic salt solution After the inflammation has subsided and the lumen of the bowel has opened up a smooth diet should be tried In order to relieve constipation the patient may take agar Heinz rice flakes or mineral oil In some cases the best results are secured with enemas of warm physiologic salt solution Whatever is done the patient should see to it that feces do not become impacted in the affected portions of the bowel It is probably much more easy for such impaction to take place when the wall of the gut is lined with pockets which serve somewhat like the laths that hold plaster on a wall An occasional dose of castor oil seems to help in some cases In others it may be helpful to give an occasional dose of bismuth which tends to fill the pouches much as Beck s paste might do

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ders' are likely to be abrupt Furthermore, as the roentgenologist palpates under the screen he may find that the wall of the gut is not so rigid as it would be if infiltrated with carcinoma

Examination of the blood may not help much because a leukocytosis can be present with carcinoma as well as with diverticulitis Similarly, there may be a moderate degree of anemia with diverticulitis just as there is with carcinoma of the descending colon

Because diverticulitis can so closely duplicate the clinical and roentgenologic and even pathologic picture of carcinoma of the colon, the wise physician will be careful not to threaten patients with certain death if they do not submit to operation Even when the abdomen is open and the lesion is palpated and looked at, the surgeon may decide that the mass is cancerous in nature and inoperable He may short circuit it and years later discover to his surprise that the patient is well and exceedingly grateful to some faith healer or some exponent of a quack cancer cure One of the leading surgeons of the United States tells how, many years ago, in the case of a wealthy woman he short circuited what he thought was a cancer but now knows was a mass of infected diverticula and thereby was responsible for the building of one of the most beautiful Christian Science churches in the country

It should be obvious that whenever any doubt remains in the mind of the physician it is well for him to reserve his opinion and to treat the supposed diverticulitis medically, watching the while with the roentgen ray If operation is done and a supposedly carcinomatous and inoperable lesion is left untouched, it is often advisable to remove a lymph node or two for microscopic examination A negative report will not prove anything but a positive one may

Aside from diverticulitis and carcinoma there are few diseases which attack the sigmoid flexure Occasionally a tumor of the ovary or some form of pelvic inflammation will cause narrowing of the lumen of the distal part of the colon, but a careful pelvic examination and a roentgenologic study of the bowel, especially after it has been filled with gas, will help to show the physician that the cause of obstruction is outside the gut

Occasionally appendicitis will produce pain in the left lower quadrant but fortunately for the diagnostician this disease usually is seen in young people who are not subject to diverticulitis In puzzling cases the ureters and kidneys must be carefully studied The lesions of chronic ulcerative colitis are likely to deform so large a part of the colon that ordinarily, the roentgenologist will have no difficulty in making the correct diagnosis

Relationship of Diverticulitis to Carcinoma — There has been a tendency on the part of some clinicians to warn patients with diverticulitis against the danger of carcinomatous degeneration in the lesions but as time goes on and opportunity is afforded to learn what happens to hundreds of these patients,

much larger than those of the first subtype Some are sessile and a single sessile growth may consist of innumerable smaller polyps

The third subtype is readily differentiated from the first by the fact that the most rudimentary characteristics of the units of intestinal mucosa persist Polyps of this type are not so easily differentiated from those of the second subtype because often they seem to represent an accentuation of the process which produces polyps of the second subtype

Third there are irregularly shaped and sized polyps from 1 to 2 cm in diameter and from several millimeters to 5 cm in length which develop in the tags of mucous membrane left after chronic ulcerative colitis has punched the lining of the bowel full of ragged holes

The origin of these polyps appears to be about as follows With the coalescence of ulcers bits here and there of the undermined walls retain their blood supply and remain as islands or bridges or dumbbell like tags Later as the ulcers heal there is proliferation of the fibroblasts and later contraction and cicatrization Elevation of the thickened and altered parts of the hypertrophied mucosa probably results in increased friction and traction against the feces with resultant stretching of the tags and the formation of pedicles

At this time these inflammatory polyps resemble closely the adenomatous ones but the dark discolorations which are so often seen in the serrated portions of the adenomatous polyps are absent Microscopically the polyps of this type will be found to be in all stages of chronic inflammation and in the serrated portions there will be numerous nests of glands seemingly caught in a network of fibrous tissue

Adenomatous changes have been observed in these polyps and in several cases observed at the Mayo Clinic the patient died with innumerable carcinomas scattered all over the inner surface of the colon

Fourth there is a rare type of polyposis in which the patient apparently inherits a colon the lining of which is covered with myriads of little teats a few millimeters in diameter and about a centimeter in length Scattered among these small polyps will often be larger ones perhaps with knob like heads hanging on a long narrow pedicle (Fig 6) On inserting the finger into the rectum the physician will gain the impression that he is feeling a rubber bath brush

One of the interesting features about this type of polyposis is that it runs in families in which several members died of cancer of the colon Erdman and Morris speak of it as the adolescent congenital or disseminated form of polyposis The polyps are definite new growths which cover the mucous membrane often from cecum to anus In some cases their knobbed heads make the bowel look as if it were covered with toadstools From the point of view of the pathologist every one of these myriad polyps can be classified under group two

Our impression from studying a number of cases of this disease is that if

Polyposis of the Large Intestine

Colonic polyps are found not infrequently during the sigmoidoscopic examination of patients and at the necropsy table These lesions have great interest for the clinician because so often they are the forerunners of cancer Because of this fact they must be looked for and studied with care

They can best be described under several headings First, there are the small polyps a few millimeters in diameter and from 5 to 20 mm in length Usually they are symptomless and are found more or less accidentally during examinations with the sigmoidoscope Rarely, if ever, are they demonstrable with the roentgen ray Sometimes they are found in a patient who suffers an occasional attack of diarrhea, but often again no history of loose stools can be obtained Although these small polyps seem to produce so few symptoms they are described first because they are the ones most commonly seen in practice

Second not infrequently at necropsy or at operation for carcinoma of the colon or during investigation of the colon for occasional slight hemorrhages from the rectum one or more adenomatous polyps will be discovered They may be from 1 to 5 cm in diameter and from 2 to 4 cm in height They may be sessile or pedunculated, and some are more or less pigmented When on a pedicle they may grow to 3 or 4 cm in diameter and from 10 to 15 cm in length

In many cases the pathologist is unable to see anything peculiar about the colonic mucosa which might account for the development of these polyps Their great importance lies in the fact that most of them are potential carcinomas and many of them are definitely malignant when first seen As has been shown by FitzGibbon and Rankin polyps of this second type may be classified under three subtypes

In the first subtype the epithelium retains its normal characteristics The tumors may be nodular or smooth and well rounded Scattered areas may be found in which there is some evidence of hyperplasia due perhaps to repeated trauma and subsequent inflammation The matrix of these polyps consists of loose connective tissue, derived from the submucosa A pedicle is always present

Polyps of the second subtype are readily distinguished from those of the first subtype by the presence of striking structural changes in the epithelium and the connective tissue The cells in the epithelium covering the polyp are hypertrophied elongated and often compressed laterally In places their over growth piles these cells into multilayered buds which may project into the lumen of the tubules as well as into the connective tissue matrix The nuclei become elongated to match the cells and the production of mucus is diminished Cystic enclosures are often seen The polyps are usually pedunculated and are often

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these patients wait long enough they will all suffer with cancer of the colon In several of our cases the patient was very willing to submit to colectomy because he knew what had happened to several of his relatives Sometimes two brothers have been in the hospital at the same time undergoing operation for cancer of the colon In at least two instances patients came for investigation of the colon solely because they feared that they might go the way of their relatives

One man aged thirty year whose only symptom was slight looseness of the bowels with occasional streaks of blood in the stools came to consult us because his mother and two brothers had died of cancer of the colon On another occasion a mother brought her boy of ten with a disseminated polyposis of the colon He had no symptoms but she feared he might be like his father who died at the age of thirty two years following a colectomy done for the relief of the same disease

Symptoms may be absent or there may be a little looseness of the bowel with the occasional passage of blood

Diagnosis

Since in the majority of cases of polyposis some of the lesions involve the rectum and sigmoid loop, the sigmoidoscope is probably the most valuable instrument to be used in making the diagnosis It helps the physician to see not only that polyps are present but also it often allows him to see that malignant changes are taking place The history will be helpful when it comes to recognizing the type of polyposis which is a sequel of chronic ulcerative colitis The double contrast method of roentgenologic examination described elsewhere in this chapter is also very helpful

Treatment

In the case of the small filiform polyps in rectum and sigmoid the best treatment is fulguration through the sigmoidoscope A roentgenologic search should be made for larger polyps or carcinomas farther orad in the colon and in every case the patient should be urged to submit to yearly examinations of the bowel

The larger polyps must always be removed surgically as soon as they are found because only the pathologist can tell how benign or malignant they are

The polyposis that results from chronic ulcerative colitis must be watched carefully At times some of the polyps that can be reached through the sigmoidoscope can be fulgurated Frequent roentgenologic examinations should be made and so long as there seem to be no increase in the size of the lesions they can be left alone and treatment can be directed toward a cure of the coli

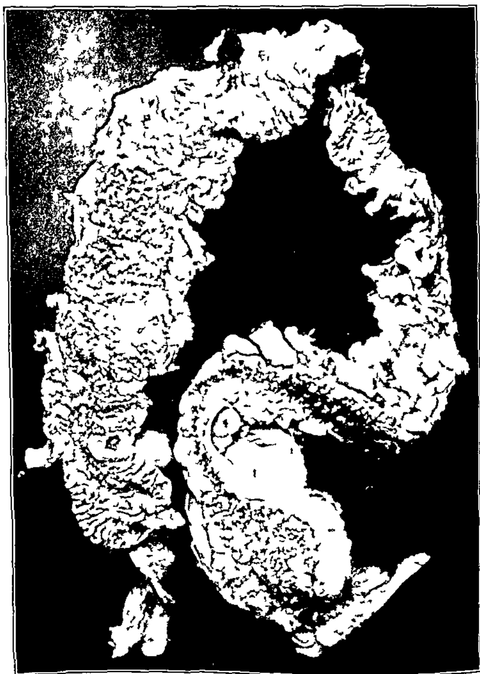


Fig 6 Iolyposı of colon of congenıtal type

sphincter of the anus but often it is orad to it The distended colon usually is enormous, and it may be from 15 to 25 cm in diameter The muscular coats are all hypertrophied and the fibrous layers are thickened When the condition has existed for some time the mucous membrane is chronically inflamed and at times much thickened and even ulcerated In some ca es atrophic changes are to be found

Etiology

The fact that in the cases of congenital megacolon there is no sign of a lesion at the point of apparent obstruction makes it seem probable that the defect must be looked for in that part of the nervous system that controls the voiding of the feces from the terminal segment of bowel

Learmonth and Markowitz have shown that immediately after section of the nerves of the inferior mesenteric plexus of the dog there is an increase in intracolonic pressure They have shown that the thoracico-lumbar segment of the autonomic nervous system provides the motor supply for the nternal sphincter of the anus and the inference is that these nerves exert a continuous tonic influence on the muscle in the terminal part of the bowel

In man, it is generally assumed that the fibers of the inferior mesenteric plexus (sympathetic) which end in the musculature of the colon and rectum carry inhibitory impulses but there is evidence to indicate that both the sympathetic and the parasympathetic nerves have both motor and inhibitory actions Persi tent clo ure of the internal sphincter of the anus might result then from a disturbance in either system of nerves or in the normal balance that theoretically exists between them

Hurst has invented the term achalasia to define a condition in which a sphincter fail to relax before an approaching wave and he believes that this is what happens in the pelvi rectal segment of the colon in Hirschsprung s disease Wade made the nervous imbalance theory seem more plausible when he reported two cases One was that of a baby six weeks of age who had recurring attacks of distention and vomiting and visible peristaltic waves in the colon The rectum was found to be empty but when the finger was passed higher a flood of feces which had accumulated in the pelvic colon gushed forth The other case was that of a child in whom a much dilated colon was excised after the ileum had first been anastomosed with the lower end of the sigmoid loop The fact that some form of obstruction remained was obvious two years later when examination showed that the last 5 cm of the ileum was so greatly dilated as to resemble the original megacolon

As Alvarez has pointed out perhaps the simplest explanation of the obstruction in Hirsch prung s disease and of the very similar contraction rings that

tis If later, after the colitis is under good control, the polyps should show signs of growing and becoming malignant, colectomy will be the only hope of the sufferer Unfortunately it is a particularly dangerous operation in this type of patient

The patients with the congenital type of disseminated polyposis generally must submit to colectomy because otherwise they are probably doomed

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J A B
W C A

Megacolon

There are at least two clinical types of megacolon, one congenital or idiopathic and the other acquired The first type which carries the name of Hirschsprung is the commoner of the two Strange to say, in these cases an obstructing lesion cannot be found at the point where the bowel suddenly narrows In the second or acquired form of the disease, the trouble can come on at any time in life as the result of some mechanical obstruction in the distal part of the colon The congenital type was first described by Parry in 1825 and later by von Ammon in 1842 but Hirschsprung s paper, written in 1886 was so complete that ever since its appearance his name has been attached to the clinical picture

The patient usually is a stunted child whose abdomen is greatly distended by a huge colon At operation or necropsy nothing wrong can be seen in the recto sigmoid region to account for the marked obstruction that evidently exist The point of obstruction appears sometimes to be located at the internal

The type of megacolon that Rankin has described is due to organic obstruction, it comes late in life but it presents clinical and pathologic features similar to those of true Hirschsprung s disease

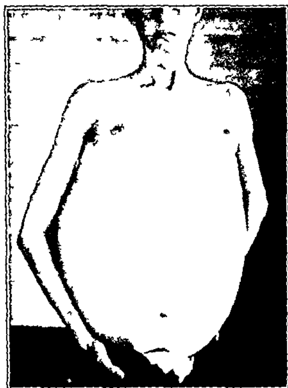


Fig 7 Hirschsprung s disease in a girl of 19 years.

Diagnosis

The history together with a glance at the patient usually establishes the diagnosis and a roentgenogram makes it doubly certain (Fig 9) The custom in many places is to demonstrate the size of the colon by the injection of a barium enema but this procedure which is likely to be followed by a hardening and caking of the retained powder is so dangerous and troublesome that it should not be permitted Instead the roentgenologist should make his examination after filling the bowel with air or preferably with oxygen or carbon dioxide which are absorbed rapidly The trouble with air is that when it is used the nitrogen in it must be evacuated as flatus

occasionally cause obstruction in the small intestine is that, in the particular segment of gut involved, there has been a failure in development of those neurones in Auerbach's plexus which are in intimate connection with the intestinal muscle fibers (Nolf Alvarez) The reason for suspecting this is that in lower forms of life, when smooth muscle is cut off from its ganglion cells, it contracts into a hard ball and stays that way This spastic contraction is somewhat similar to that which is so commonly seen in the arm and leg of a man who has suffered a cerebral apoplexy

Ogawa inclines to this theory, and there is some evidence for it in a paper by Dalla Valle who reported his inability to find any sign of nervous tissue in the contracted sigmoid colons of two brothers operated on for megacolon The way to test this theory is to excise, whenever surgically possible, the contracted segment of bowel and to see if the obstruction disappears just as it does in the case of the contraction rings in the small intestine Whenever possible, also sections from these contraction rings should be turned over to a neuropathologist for study Unfortunately the staining of Auerbach s plexus is so difficult and uncertain that only an expert can trust his findings

Symptoms

Megacolon may be present at birth and peristaltic waves coursing over a distended abdomen may be evident in the first week of life In other cases, the deformity develops gradually during infancy There are milder grades of the disease in which the only things noted by the mother are a large abdomen and a growing tendency to constipation Often, with this type of megacolon, the patient is not taken to see a consultant until he or she has reached the second or third decade of life

The remarkable feature in some cases is that in spite of the fact that for months these children have been carrying around large masses of feces, they show but few signs of either intoxication or reverse peristalsis There are none of the symptoms which appear so promptly in cases of obstruction of the small bowel Only at times will there be attacks in which back pressure is evidenced by vomiting and only occasionally does a severe form of toxemia appear Emaciation, anemia, a sallow complexion, anorexia and lassitude are complained of by some of the patients but in many of them the only troublesome feature is the much distended abdomen

Children with megacolon can go for weeks and months without a movement of the bowels In one case that of a girl nineteen years of age the bowels were moved once in two or three or four months, and on one occasion she went six months without difficulty (Figs 7 and 8) Because of the great distention of the abdomen these children show a peculiar outward flaring of the lower ribs

At the Mayo Clinic we have found that even the most markedly distended colon can be cleaned out by a combination of two modes of attack. First the food given must be almost without residue. The type of diet used has been described in the section on preoperative treatment of carcinoma of the colon.



FIG. 9 Roentgen ray picture of megacolon

Second cleansing enemas of warm physiologic saline solution should be given two or three times a day. A small daily dose of some laxative such as senna will help in emptying the bowel.

Dilatation of the so-called pelvirectal sphincter with the help of a rubber

Treatment

Many forms of treatment have been tried, most of them without much success Therapeutic efforts can be made along either medical or surgical lines The first thing to do when a child comes in is to try to empty the bowel and



FIG 8 The same girl after the colon was cleaned out.

then to see whether the mother can keep it fairly empty with a reasonable amount of effort If in spite of all her care, the colon becomes markedly distended again, some form of operation must be considered Before any operation is tried the colon must be cleaned out even more thoroughly than it is during attempts at treatment

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J A B
W C A

Constipation

Definition

The term constipation is commonly used to denote a condition in which either defecation occurs with insufficient frequency or else the stools are insufficient in quantity or abnormally hard and dry and difficult to pass In some cases the difficulty in evacuation is associated with the breaking up of the fecal column into small ovulated masses which are harder to extrude than is one large sausage like mass

When a person complains of constipation he may mean one of several

bag has been attempted by Fullerton with some encouraging results We have not tried it Diathermy of the abdomen has been tried by Amberg and has given good results in a few cases Usually medical measures require a great deal of effort and the patient has to be in the hospital The trouble is that after a time both physician and patient become tired and discouraged over the amount of effort required to keep the bowel clean, and an operation has to be considered

Many surgical measures have been tried in the past, such as cecostomy colostomy and colectomy, but most of them have been abandoned on account of the poor results obtained In recent years, following the suggestion of Wade and Royle of Australia, Judd and Adson and Rankin and Learmonth have performed lumbar sympathectomy with encouraging results As Rankin and Learmonth say Even if, in our ignorance of its ultimate cause, we cannot attack the disease directly we may still carry out flanking attacks in three directions (1) we may attempt to diminish the dilatation of the colon, (2) we may try to leave its motor nerves in less disputed control, and (3) we may attempt to relieve any opposition to the expulsion of the content of the bowel offered by the internal sphincter of the anus If our anatomic and physiologic reasoning is correct, we can accomplish the first and second objects by division of the inferior mesenteric nerves, and the third by division of the presacral nerve"

All of the patients in whom some type of neurectomy has been tried at the Mayo Clinic have received benefit, and a few apparently have been cured If the greatest success is to be obtained it seems probable that even after operations much care should be taken to keep the bowel clean Even if a neurectomy were to remove immediately every bit of obstruction in the rectal region, one could hardly expect the operation immediately to restore the functions of a huge thick walled colon, which has been stretched out of shape and severely injured

The relief of the acquired form of megacolon depends, naturally, on the removal of the causative obstruction whatever it is

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for four days and had themselves roentgenoscoped at intervals there was never any sign of a return of fecal material into the small bowel

To the patient the reassuring point about all this is that he can stop worrying about abnormal conditions in the small bowel and can remember that stagnation is taking place only in that terminal segment of gut which was specially designed by the Creator to cope with it Furthermore when the patient knows that the constipation is entirely colonic or rectal he will be less inclined to upset digestion in the small bowel by the taking of purgatives and rough diets and more inclined to wash the bowel out from below

Types of Constipation

It is always important to find out how long the so-called constipation has been present because naturally if the bowels have been sluggish for years the symptom is not so important as it is when it has but recently appeared Particularly in a person past middle age the constipation that comes suddenly out of a clear sky after years of perfect intestinal behavior is a symptom that should cause the physician great uneasiness Such recent constipation is even more alarming when there have been episodes in which the bowel was more or less obstructed and during which there were colicky pains distension of the abdomen and loud gurgling noises

In a few of the cases in which the patient complains bitterly that the bowel movements are insufficient in number or size or unsatisfactory in shape or color the main defect appears to be in the brain and the physician should soon recognize the fact that he is dealing with a colonocentric psychopath similar to the one whose whole attention is concentrated on his heart or on his sexual organs These people usually are hopeless and the physician will probably do well not to waste time on them

There is one type of constipation which alternates with diarrhea In some of these cases the constipation seems to be primary and the diarrhea results from an irritation of the bowel produced by decomposing feces In other cases the diarrhea seems to be primary and what is called constipation is the natural result of a too complete emptying of the colon

Causes of Constipation

Unfortunately in most cases of constipation the cause is not clear In the first place there appears often to be a pronounced inherited predisposition this sometimes is so strong that it shows up in infancy and childhood

Constipation is probably more commonly met with in frail flabby sickly women than in any other type of humanity In these women the poor colonic

things If he happens to have been reading a certain type of advertising pamphlet, he may mean that he has only one good bowel movement a day, and he thinks he should have three Again, he may mean that a laxative has been taken every night for twenty years or more obviously in such a case the patient cannot be sure that he is constipated because he has never stopped to see Still another person complains of constipation because the bowels move only once or twice a week, but in him careful study may show that this is normal and not worth fussing about In another person the cause may be starvation due to lack of funds, to finickiness, or to an obstructing lesion at the pylorus Here again, the lack of bowel movements is to be expected, and the term constipation should not be applied

According to Hurst a person may be considered constipated if the bowels are not opened at least once in every forty eight hours, but this is not a safe definition because it is common to see persons whose bowels move four or five times a day but who still are suffering from a sluggish and badly overloaded colon In a normal defecation the left half of the large bowel probably should be evacuated, but in the troublesome cases just mentioned only a little material comes away each time from the rectum, and the patient still feels uncomfortable and desirous of a bowel movement In other words, the constipation is cumulative and in spite of frequent daily bowel movements the patient finds himself compelled to take a laxative or an enema every two or three days

For years it was customary for textbook writers to divide all cases of constipation into the atonic and the spastic but I agree with Hurst that there is no factual basis for doing this and no advantage to be secured therefrom In practically every case of constipation the roentgenologic examination of the colon shows the haustration to be unusually well marked in fact the bowel appears to be contracted and spastic even in the thin flabby type of woman in whom one would expect to find atonic constipation if it is ever to be found anywhere

Another definition of constipation given by Hurst is that it is a condition in which none of the residue of a meal taken eight hours after defecation is excreted within forty hours Again it is questionable whether any such exact limits of normal can be placed on the motility of the colon As will be shown later, the rate of progress of material through the bowel varies markedly in normal persons

When it comes to treating constipation, it is often helpful to impress the patient with the fact that in constipation the stagnation is always in the colon, distal to the ileocecal sphincter In twenty two years I have never seen a case of ileal constipation Furthermore, when Donaldson and his associates eating each day food containing barium, voluntarily restrained their bowel movements

There is no question that one of the commonest causes of constipation is nervous tension As everyone knows this is associated with an increased tonus of the voluntary muscles a mild spasm which apparently involves the anal sphincters and makes it hard for the feces to enter the anal canal Many a man or woman who is badly constipated while working at high tension in the city will have perfectly normal bowel movements when loafing on a vacation As a patient once said to me Doctor if I could only get the requisite amount of excitement out of my life my bowels would be all right When I am badly worried I have diarrhea and when I am moderately worried I have constipation To a large extent then constipation appears to be a disease of civilization and of brain workers So long as men jump up from the breakfast table and rush for a commuting train or a subway some of them must accept constipation as the inevitable result of an abnormal life That one's mental reaction have something to do with constipation is perhaps indicated also by the fact that some insane patients tend to suffer with severe constipation during their periods of depression

As many writers have pointed out it is probable that constipation often arises because a person fails to respond promptly to the calls of Nature and thereby accustoms the rectum to the presence of feces Another cause of constipation which one finds in civilized communities probably is lack of exercise There is no question that movements of the body and of the abdominal muscles tend to stimulate peristalsis and the constipation of the bedridden is well known It must be admitted however that one can find much constipation among farmers and laborers and even among professional athletes In some cases strenuous exercise during the summer months with the associated profuse perspiration may lead to constipation perhaps on account of the diversion of water away from the bowel and into the skin

In some cases the nature of the diet has much to do with constipation I have heard Stefansson say that until the Eskimos began to live on the traders groceries they did not know what constipation was Actually we know that the fat which constitutes so large a part of the diet of the uncivilized Eskimo is much more laxative than the starch and sugar which we use for bodily fuel in the United States and England

The fussy invalid who has a poor appetite and who eats very little must often be constipated because there is so little residue left for the colon Similarly, the person who lives on concentrated foods or foods which leave little residue in the bowel should be predisposed to constipation Infrequent bowel movements are to be expected also in persons who are starving themselves to avoid the pains of a perforating duodenal ulcer or a cancer of the stomach In such patients the sluggishness of the bowel is due not only to the lack of food but also to the fact that the obstruction at the pylorus causes the chyme to

function is often supposed to be due to a flabbiness of the muscles of the colon, but my impression is that it is due more to a lack of proper coordination in the muscles involved in the defecatory act This disturbance has been called by Hurst dyschezia, or an inability to defecate

In trying to explain the presence of constipation many physicians are inclined to emphasize the importance of ptosis of the colon Actually it is doubtful if the ptosis is an abnormality and if it is, it is hard to see how the position of a muscular tube in the abdomen can affect its power to propel its contents When Moody showed in over 1 000 young athletes and healthy college students that the commonest position of the colon (with the person standing) is in the true pelvis it became obvious that what is commonly looked upon by physicians as a serious defect must be normal Certainly it is compatible with perfect health and good defecatory habits Some physicians still contend that this ptosis, while not necessarily productive of constipation, predisposes to it The answer to this is that it is hard to prove that the constipation is not due to nervous and dietetic causes

Some writers feel that it is highly important that the bowel be fastened firmly to the posterior abdominal wall but actually, all research work done on the subject has indicated that the abdominal contents all have about the same specific gravity as that of water and as a result they may be said to float all together in the abdominal cavity The viscera are not held up by their guy ropes, but instead one floats on top of the one below, and with the man or woman in the erect position the lowermost organs rest on the pelvic floor the ilia and the lower part of the anterior abdominal wall If anyone doubts this let him inject 2 liters of oxygen into the abdomen of a man and then let him look at that man in a vertical fluoroscope

In some cases the physical basis for an inherited predisposition to constipation is to be found in the large size and capacity of the colon One occasionally finds an adult with a colon so large that one wonders if he is not suffering with a mild form of Hirschsprung s disease Obviously such a large colon must take several days to fill to the point where it can overflow In other cases it is possible that the whole bowel is so thrifty in its absorptive processes that little residue is left from which to form feces

That there is a tremendous tendency to constipation in some persons is shown by the fact that years ago when colectomy was fashionable it was found that some of the patients so treated promptly developed constipation in the terminal ileum I know of one case in which this stagnation became so marked and the difficulty in emptying the bowel so great that every year or so the patient had to return to the surgeon for the removal of the short segment of ileum next to the stoma This was always found to be markedly hypertrophied

yet there was no constipation Such cases show how powerful the colonic musculature is and how well able to empty the lower part of the bowel if only the defecatory reflexes are normal

One would expect all persons with painful and spasmogenic lesions about the anus to suffer from constipation and actually many of the sufferers from hemorrhoids and anal fissures and fistulas are constipated Unfortunately they do not all get relief when the proctologist has cleared up the local disease

In many cases constipation is associated with a tight anal sphincter and some thing may perhaps be accomplished by moderate dilation of the muscle Some proctologists believe that abnormalities in the valves of Houston also lead to constipation

Many physicians throw the blame for constipation on kinks and adhesions but I doubt the reasonableness of this because I know how easy it is for a moving column of fecal material to straighten out and pass around a kink and occasionally I see at necropsy or at operation a large mass of firm adhesions in a person who has not suffered from constipation Occasionally in rare cases constipation is due to the presence of a large polyp or an enterolith in the colon

In some cases constipation seems to be due to the presence of a large hernia to weakness of the abdominal muscles or to the presence of a rectocele which causes the feces to try to leave the body by way of the large blind pouch that bulges into the vagina

In some persons the difficulty in defecation is due to the presence of unusually bulky fecal masses In some women these masses are eight or ten centimeters in diameter It is probable also that many sufferers from constipation could empty the bowel more easily if the toilet seat were to be made lower or otherwise more comfortable

Physiology of the Bowel

Before describing the symptoms of constipation and before taking up questions of treatment it will probably be helpful to give a brief outline of that part of the physiology of the digestive tract which is concerned with the formation of feces and the evacuation of the bowel

It is obvious that before the physician can deal intelligently with the problem of stagnation in the colon he ought to know something of the normal variations in the rate of progress of food residues in healthy persons whose bowels move satisfactorily every day In the past most writers have assumed that the residues from any one meal leave the body within twenty four hours This has been unfortunate in that it has caused many persons much needless worry about their inability to secure a daily evacuation

Actually the studies of Alvarez and Freedlander on a number of healthy

trickle so slowly into the duodenum Normally the semi-digested food is injected somewhat forcibly into the duodenum and this stimulus commonly gives rise to a wave of peristalsis which runs down the bowel As everyone knows, bowel movements are likely to occur following the eating of a meal They are most likely to occur after the morning meal because during the night the bowel becomes rested and the reflexes that bring about peristalsis get on a "hair trigger

It is probable also that in some cases constipation is due to spasm in the bowel brought about by the taking of certain foods to which the patient is sensitive Occasionally one will see a patient who says that he is constipated only when he drinks milk or eats some food such as eggs or tomatoes or chocolate, to which he is sensitive This is a field of dietetics in which further study is needed

It is possible that in some cases constipation is due to an insufficient amount of water in the diet One of the principal uses of the colon is to return water to the body, and certain observations have led me to believe that when there is a great need for water in the tissues of the body the colonic mucosa becomes even more efficient as a drying agent, and fluids which might otherwise have remained combined with the cellulose and pectins and other hygroscopic materials in the feces are perhaps stolen away A deficiency in the amount of fat in the diet may also predispose to constipation

There are a number of conditions in which constipation is more likely to occur Thus, it is common in the aged It is likely to appear also during the course of fevers when probably the gradient of intestinal forces is flattened It is seen sometimes in the obese and in patients who are myxedematous As I have said before it is likely to be severe in the melancholic

Constipation is commonly associated also with cholecystitis, in which case it is due perhaps to the tendency to spasm which can be noted in the musculature of the whole digestive tract It is seen sometimes in cases of chronic appendicitis where it may be due to spasm at the ileo cecal sphincter and the resultant slowing of the passage of food residues from ileum to colon

Constipation is likely to be present with any chronic debilitating disease As is well known it is a salient symptom of lead poisoning It is often present in those cases of tuberculous enteritis in which the disease is sufficiently extensive to produce spasm of the bowel but not extensive enough to produce diarrhea It is severe of course with obstructing lesions in the bowel such as carcinoma of the colon, and it is often seen in cases of diverticulitis

In some cases constipation seems to be due to the pressure on the rectum of a large pelvic tumor In other cases it is supposed to be the result of pressure on the colon produced by a retroverted uterus, but I doubt this, because in some women I have seen the pelvis filled with a large fibromyoma of the uterus and

copious movements need not be given oftener than two or three times a week furthermore the person who purges himself and then wishes to get back to normal must be content to wait a day or two for his next bowel movement

According to many students of the subject barium taken by mouth begins to reach the cecum in from two to four hours and leaves it in from four to twelve hours There are however wide individual variations

In man the material coming from the ileum seems to be pushed ahead through the cecum and ascending colon without the help of any peristaltic waves that can be seen on the fluoroscopic screen At intervals during the day there are what are called mass movements The haustrations in the middle of the transverse colon disappear and the fecal material runs together into a sausage like bolus some 15 cm in length A contraction ring then appears orad to this mass and in the next four or five seconds pushes it into the descending colon or into the rectum Such waves are likely to be associated with a peristaltic rush down the small bowel and they not infrequently result in a call to defecation If the call is ignored a certain amount of fecal material may be transported back again as far as the transverse colon

The reverse peristalsis which can be seen so easily in the right half of the colon of the cat can hardly be important or worth talking about in man because it is so seldom seen The colon is a sluggish organ supplied with a type of muscle that is powerful but not easily brought into action

Unfortunately we do not know enough yet about the nervous mechanisms that underlie the act of defecation There is much evidence to show that the rectum possesses a high degree of automaticity as revealed by the fact that it suffers much less than does the bladder from lesions of the spinal cord The most severe disturbances are produced by destruction of the afferent nerves from the anal region because then the animal or man cannot detect the presence of fecal material in the rectum and there is nothing to start the chain of reflexes that bring about defecation

It is possible that in some cases constipation is due to the fact that spasm about the sphincters interferes with the descent of the fecal column into the anal canal Someone has said that defecation somewhat resembles the swallowing of a pill, if one can only get it past a certain point on the back of the tongue it can no longer be recovered, and the movements of swallowing become inevitable This is not quite true in regard to defecation, but I think there is something of value in the simile

Symptoms

The symptoms of constipation vary in different persons In most of them the filling of the rectum does not produce any sensations beyond perhaps a

medical students showed that the rate of progress of residues through the bowel varies markedly in different persons. They gave to each student a capsule containing 50 tiny glass beads and counted the number of these beads passed with the feces each day. They found that in twenty four hours these young men, every one with a satisfactory daily bowel movement did not pass 100 per cent or anything like 100 per cent of the beads. There were two men who passed about 85 per cent in 24 hours but in these two the feces were soft, voluminous and badly fermented. Most of the students took four days in which to get rid of 75 per cent of the beads and there was another group in which from 50 to 60 per cent of the number were passed in 9 days. Most of the students passed about 15 per cent on the first day and 50 per cent more the second day. As Hoelzel has pointed out such glass beads, which are a little heavier than fecal material tend to lag slightly behind the main current in the colon, but I am sure that this error is not large enough to invalidate the conclusions which must be drawn from the experiments just quoted.

At first sight it appeared that the results of this investigation must be in conflict with the daily observations that every roentgenologist makes with barium meals but when Alvarez and Freedlander actually measured the fractions of a barium meal passed in successive days they found that the excretion varied much as it did with the beads. In some of the students the drug acted much as would a big dose of agar or liquid petrolatum, and most of the material was voided in the first 24 or 48 hours. In another group barium containing feces continued to come away for a period of a week or more and as any roentgenologist could have prophesied some of it was still present here and there in the haustra of the colon ten days and longer after the ingestion of the meal.

The most important lesson learned from these studies was that whenever, in one of the students the bowel was thoroughly emptied as by a cathartic or a transient diarrhea, there were either no movements at all or else very small ones for two or three days thereafter until the colon had filled again. The colon may perhaps be likened to a railroad siding on which there stand three freight cars. Every day a new one arrives and bumps the end one off so as to leave three again. Occasionally one arrives with such force that it bumps all three off, and then two or three days have to elapse before the siding again is full enough so that a car arriving at one end can push one out at the other.

Since the fecal material is soft and mushy in the cecum and ascending colon, a man may know that when the end portion of the formed stool which he passes is soft, his colon has almost certainly emptied itself sufficiently for that day. It appears from the studies with the glass beads that each day approximately one sixth of the material that arrives from the ileum goes on down the colon together with about half of the feces that have been held over in the cecum.

The lesson to be learned from all this is that a purgative that produces

copious movements need not be given oftener than two or three times a week, furthermore the person who purges himself and then wishes to get back to normal must be content to wait a day or two for his next bowel movement

According to many students of the subject barium taken by mouth begins to reach the cecum in from two to four hours and leaves it in from four to twelve hours There are however wide individual variations

In man the material coming from the ileum seems to be pushed ahead through the cecum and ascending colon without the help of any peristaltic waves that can be seen on the fluoroscopic screen At intervals during the day there are what are called mass movements The haustrations in the middle of the transverse colon disappear and the fecal material runs together into a sausage like bolus some 15 cm in length A contraction ring then appears orad to this mass and in the next four or five seconds pushes it into the descending colon or into the rectum Such waves are likely to be associated with a peristaltic rush down the small bowel and they not infrequently result in a call to defecation If the call is ignored a certain amount of fecal material may be transported back again as far as the transverse colon

The reverse peristalsis which can be seen so easily in the right half of the colon of the cat can hardly be important or worth talking about in man because it is so seldom seen The colon is a sluggish organ supplied with a type of muscle that is powerful but not easily brought into action

Unfortunately we do not know enough yet about the nervous mechanism that underlie the act of defecation There is much evidence to show that the rectum possesses a high degree of automaticity as revealed by the fact that it suffers much less than does the bladder from lesions of the spinal cord The most severe disturbances are produced by destruction of the afferent nerves from the anal region because then the animal or man cannot detect the presence of fecal material in the rectum and there is nothing to start the chain of reflexes that bring about defecation

It is possible that in some case constipation is due to the fact that spasm about the sphincters interferes with the descent of the fecal column into the anal canal Someone has said that defecation somewhat resembles the swallowing of a pill if one can only get it past a certain point on the back of the tongue it can no longer be recovered and the movements of swallowing become inevitable This is not quite true in regard to defecation but I think there is something of value in the simile

Symptoms

The symptoms of constipation vary in different persons In most of them the filling of the rectum does not produce any sensations beyond perhaps a

feeling of fullness and pressure in the pelvis, but in a few the distension of the bowel produces a feeling of irritability and poisoning, mental activity is slowed and made difficult and headache appears In the worst cases the patient is so distressed that he or she keeps taking enemas or laxatives throughout the day, and little else is thought of beside the unpleasant sensations coming from the bowel

In another large group of patients the main symptoms are those of indigestion flatulence and back pressure from the bowel toward the stomach The *patient has little appetite or he seems to fill up quickly on starting to eat* the tongue may be coated, and there may be a bad taste in the mouth In occasional cases there is a distress which comes on around eleven in the morning and five in the afternoon and which can sometimes be relieved by the taking of food or the chewing of gum This distress appears to be due to the fact that three or four hours after a meal the ileum finds itself full and unable to push its contents into the overly filled and irritable cecum It can do this only with the help of the stimulus that comes from repeated swallowing or from the taking of more food into the stomach

In other cases the stagnation of fecal material in the cecum produces some typhlitis and a syndrome which suggests the presence of chronic appendicitis Sometimes if the stagnation is not relieved the colonic mucosa becomes irritated or ulcerated and diarrhea results

As is well known, constipation will at times seem to bring on an attack of "mucous colitis The passage of large hard fecal masses may produce fissures of the anus and may irritate hemorrhoids

It is commonly believed that chronic constipation can lead to the production of hypertension arthritis and many other chronic diseases, but as yet there is little reliable evidence of such associations Alvarez McCalla and Zimmermann showed that there is no relation between constipation and hypertension In twenty five years I have seen one case in which there appeared to be a definite relation between constipation and arthritis and in which ileocolostomy worked a cure I have seen many more patients who believed that their joints would be well if they could only get the bowels to move normally, but in most of these cases I was not convinced because the daily cleansing of the bowel with large enemas failed to bring much relief

Methods of Study

During the examination of the patient it will often be noted that the descending colon feels as hard as if it were a solid rod of muscle The cecum will often be rather large and full of gas and fecal matter Often, and especially in nervous women the whole colon will be sensitive to the touch

In all cases of constipation a rectal examination should be made first with the finger and then with the anoscope and sigmoidoscope The finger will often be gripped firmly by an abnormally tight anal sphincter Occasionally the anoscope will show a badly inflamed and widened anal ring with much cryptitis It is in this type of case that I have seen the greatest benefit follow from the efforts of the proctologist

Especially in cases in which the constipation has come recently and is proving intractable a careful roentgenologic examination of the colon must be made Ordinarily this is done with the help of a barium enema The opaque material should be watched as it flows in and then films can be made

Sometimes with a barium enema it is difficult to be sure of the condition of the cecum and then it is well to give a barium meal and watch the entrance of the material into the large bowel

In some cases it is well to study the cholecystogram and also to check the condition of the stomach and the pylorus Sometimes with the aid of the barium meal it is helpful to find out where most of the stagnation takes place that is whether it is in the cecum or in the rectum I can remember the case of a child with a severe constipation which was refractory even to the use of strong purgatives When the pediatrician learned that after 18 hours nearly all of a barium meal was in the rectum the treatment was promptly changed and the child soon recovered with the help of measures directed toward the cleansing and reeducation of this terminal segment of the colon

Treatment

It is obvious that intelligent treatment must be preceeded by a careful study of the particular problem presented Thus if a woman has been taking a teaspoonful of cascara extract every night for ten years the physician can do either one of two things he can either dismiss the patient with the injunction to thank God that her constipation is so easily controlled or else he can ask her to leave the bowels alone for a few days to see what will happen If like a good Christian Scientist she can stop taking medicine and stop worrying she may find that she is well Perhaps when left to themselves the bowels will move only twice a week but if this does not cause any discomfort the new schedule should be accepted as normal and nothing more should be done about it This is particularly true when the patient lives on next to nothing Similarly it is a shame to treat with purgatives the so-called constipation that results when the patient is being starved by the inability of food to pass an obstructing lesion at the pylorus

In many cases the physician must begin the treatment of constipation with reassurance and with attempts at the casting out of that fear of auto-intoxica

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through the wall of the digestive tract to injure the patient Infants and children certainly appear to be poisoned during the course of diarrheas but evidence is accumulating to show that in these cases and in many others it is not a toxin that reaches the blood stream but a living bacterium

It has been well proved that even in health bacteria are constantly going through the intestinal mucosa most of them are stopped in the neighboring lymph nodes but some go on through into the liver and perhaps even into the general circulation This passage of bacteria into the blood stream takes place more easily after purgation and in the presence of diarrhea when holes are opened up in the mucous membrane and when most of the bacteria in the bowel are living and virulent In the presence of constipation the feces are so solid and dry and so lacking in nutriment that most of the bacteria die Furthermore it is obvious that little absorption can be expected from solid masses of fecal material For this reason most students of the subject of auto-intoxication have actually come to the conclusion that man is safest from poisoning when he is constipated[1]

It is helpful to point out to an intelligent patient that few of the poisons that are known to be formed in the bowel can pass unchanged into the portal circulation Most of them are stopped or chemically altered in the wall of the bowel and those that get through are likely to be destroyed or changed in the liver or in the capillaries of the lung Furthermore any toxin that can get past these several filters must trickle into the general circulation so slowly and in such small doses that physiologic effects cannot be produced A patient will understand this if he is reminded that if he were to divide an aspirin tablet into 100 tiny doses to be taken at short intervals during the course of a day he would never relieve his headache the drug would not reach the brain in sufficient concentration to have any effect and besides it would be changed or excreted almost as fast as it entered the body

Finally the physician can assure the patient that there is no reliable evidence to indicate that anyone ever suffered serious injury to the brain or any other part of the body on account of constipation Anyone who has seen many children and youths with Hirschsprung s disease with the huge abdomen containing several liters of fecal matter and yet with a clear skin and no complaint of headache or arthritis or hypertension or epilepsy must have marveled at the efficiency of the mechanisms with which we are endowed to protect us from the absorption of toxic material

In many cases then the treatment of constipation will consist largely of psychotherapy Not infrequently the patient who has tried many treatments will go to some specialist or some large institution with the determination that at last he is going to stop the use of palliatives and cost what it may he is going to find the cause of his trouble and have it radically removed In most

tion which so often haunts the patient and makes him too fussy about his bowels If there is no distress when the bowels are left bound for a few days, the patient may easily be induced to adopt a new schedule and to try for a movement perhaps twice a week If, however, the failure to secure a bowel movement is promptly followed by the appearance of dopiness, dizziness and headache the treatment has to be more energetic

Before the physician can calm the fears of the woman who is sure that intestinal auto intoxication is eventually going to injure her brain and joints and arteries he must find out how soon after defecation her relief comes If, as almost always happens the patient says that the relief comes in a minute or two then the physician can point out that in this case the symptoms cannot be due to the presence of a toxin passing from the bowel into the blood If this were the mechanism involved surely relief could not come so quickly, it could come only after most of the poison had been destroyed and excreted from the body To use an easily understandable simile, a drunken man is not sobered the moment his flask of whiskey is taken away from him

But the symptoms are real and if they are not due to chemical poisoning what are they due to? In the particular cases in which the patient gets relief immediately after a bowel movement, and only in these cases, the physician can be sure that the distress is produced mechanically, and that it is due to distension of the rectum and pressure on sensitive nerve endings Actually, one can sometimes show this in some of these highly sensitive persons by distending the rectum with cotton or air As Ivy has pointed out, this experiment is not successful in the average person but one would not expect it to be because every gynecologist knows that in many women the rectum is distended with fecal matter which does not give rise to any distress In most persons, then, the rectal mucosa must be fairly insensitive it is only in a certain group of people that this part of the bowel is so closely coupled with the brain that distension produces mental distress What is more, even in these highly sensitive persons there are times when the filling of the rectum does not produce the characteristic sensations

The physician must often discuss these facts with the patient before he can hope to drive out fear and until he does drive it out, he cannot hope to get the patient to leave the bowel alone long enough to know what it can do by itself It is often helpful also to show patients how difficult it is for poisons to get from the lumen of the colon into the general circulation in doses large enough to produce symptoms It must be admitted that auto intoxication of intestinal origin is a possibility, it cannot be ruled out entirely and it seems probable that poisoning of some kind must take place in cases of diarrhea in which the intestinal contents are liquid and more easily absorbed by the mucosa Furthermore we know that highly toxic substances formed outside of the body can get

easily discouraged when the patient says 'I cannot take laxatives I cannot take roughage and I cannot take enemas' A little investigation may show that all these therapeutic measures have been used wrongly

Laxatives — The fashion at present is to decry the use of chemical irritants and to favor the use of mechanical ones Obviously of course when a patient can overcome constipation by taking each day more fruit or vegetables or fat there is no sense in taking chemical laxatives but when as often happens the large amount of indigestible material added to the diet causes flatulence and abdominal discomfort a small chemical irritant may be preferable

Every physician of experience has met women who have taken the same dose of cascara every night for many years and apparently with entire satisfaction To my way of thinking these women deserve congratulation and not censure Other persons less fortunate cannot take any type of laxative with any degree of comfort Perhaps the medicine works well for a while and then the dose must be greatly increased or it may be impossible to find a dose that will give a good result either the action is too violent or else there is none at all In other cases the laxative produces flatulence or abdominal and rectal discomfort

In my experience the most useful laxative for patients with a sensitive type of colon is calcined magnesia Some of them however prefer cascara sagrada senna or phenolphthalein and others do well with one of the many commercial mixtures of laxative salts There are a few fortunate persons who can get relief simply by drinking before breakfast four or five glasses of physiologic saline solution

Some of the old English physicians based their practice on a theory that sounds plausible In attempting to avoid the over purgation produced by one large dose of a drug they divided the medicine into three fractions and prescribed one to be taken with each meal When a patient is willing to take the trouble the experiment can be tried, it sounds promising but I haven t much experience with it

One of the most useful hints in regard to the taking of chemical laxatives is to ask the patient to take them only two or three times a week As has been shown elsewhere in this section after a thorough cleansing of the colon there is no sense in demanding a bowel movement on the next day or even on the day after that If the patient does not feel distressed he should not take a laxative again until two days have passed Taken at intervals in this way there is less likelihood that the drug will lose its effect and that the dose will have to be increased I shall not go into a detailed description of laxatives because such information can easily be found in books on pharmacology

Belladonna is used extensively by physicians with the idea of relieving spasm in the colon Experimental work indicates that the effect of the drug on the

cases such a patient is likely to leave the office of the consultant disappointed and disgruntled unless the situation is carefully and tactfully explained to him In many cases he must be made to see that his troubles are due to his abnormal way of living If he could lead an easy going outdoor life, he would probably be all right but so long as he is compelled by necessity to lead the harassed life of a business man, rushing each day from a suburban apartment to a city skyscraper and back again, the colon is not going to empty itself unless it is helped in some way

Obviously there are only two main ways in which the fecal column can be influenced it can either be driven down from above, or else washed out from below Furthermore there are two main forms of stimulus that can be applied from above, one, a chemical, the other a mechanical one, in other words, one can use laxatives of some kind, or one can fill the bowel with indigestible material

One might in addition, ask a surgeon to shorten or short circuit or remove the colon or to cut the sympathetic nerves supplying the internal sphincter of the anus, but these are serious measures which would be bad enough if they always worked Unfortunately, experience has shown that too often they fail to bring permanent relief

The patient will see then that he is facing a mechanical problem and one that cannot be solved without intelligent cooperation on his part He will see that there is no new or royal road to recovery and he will be more willing to work with the physician to see if he cannot take up again some of the methods which he has worn out or discarded as useless and, by improving the technic, turn failure into success

Thus laxatives that did not work well or were soon ineffectual when taken every day may be found to work like a charm when taken twice a week, or a small dose taken twice a day may work better than a large one taken once a day Or it may be found that a small dose of some mild chemical irritant is less troublesome and less harmful to digestion than is a large dose of some rough mechanical irritant Perhaps a smoother less irritating bulk producer can be found, and in many cases an enema of warm physiological saline solution will work perfectly when enemas of soapy water only caused more distress

In other words patients with constipation must not all be treated in the same way, the physician must study individual problems, and he must then take time to describe in detail the necessary technics It is surprising how many patients do not know how to do so simple a thing as to take an enema Perhaps, if left to the guidance of some old grandmother they would do it properly and effectively but unfortunately many advisers have told them many foolish things and as a result a procedure which might be so simply and easily carried out becomes a sore trial The physician therefore must not be too

It is well when a patient complains of vague indigestion to ask if he is taking large amounts of mineral oil and if so to interdict it for a while to see if by any chance it is causing the symptoms complained of It is curious that physicians daily warn patients against eating cold greasy food and then tell them to eat their food and afterwards smear it over with cold indigestible oil Theoretically such oil should do even greater harm than can be done by the much more digestible fats of animal and vegetable origin

Enemas —Often one sees patients who say that they have gotten to the end of their rope in the treatment of constipation the variou laxatives and bulk producers have all been tried and worn out and the patient doesn t know where to turn for help In many of these persons the indigestion complained of appears to be due to back pressure from the overly loaded and *irritated colon* and sometimes a particularly intelligent patient will say, If only you could get that fecal plug out of my bowel without still further upsetting my digestion I would be perfectly well and happy I usually say to such a person that the logical thing to do would be to wash out the plug from below and he generally returns one of three answers He may say Yes I know that enemas work perfectly and I would like to use them but my physicians have all warned me against their use and have threatened me with dire disaster if I continue

Now why should they do this? As a student of medical history and folk lore I have been hunting for years for the origin of this phobia but without success It appears to be something like our fear of red meat in the presence of illness I suspect that the prohibition of enemas is based largely on the dislike physicians so often evince for the well known type of enema taking neurotic woman who suffers with mucous colitis and loves to describe the size shape, consistency and odor of the stools obtained A review of the only piece of scientific work that I know of undertaken to see if enemas are harmful left me with the feeling that they are not Even with irritant medicated enemas the changes observed by Friedenwald and Feldman in dogs seem to me to be too slight to be of practical significance Unfortunately, in their experiments they did not study the effects of enemas of physiologic saline solution I cannot see how such an inert substance could ever do any harm and practically in twenty years I have not been able to find a person in whom I could say that enemas had probably worked an injury

The second answer given by many patients is that enemas work well but they are too much trouble and take too much time On questioning these persons one generally finds that some physician has taught them first to insert a long colonic tube second to take the enema lying supine or with the hips elevated and third to hold the water for as long as possible All of these instructions seem to me not only to be useless but wrong Every well read physician should know by now that a colonic tube thrust blindly in only curls

bowel is a transient one, and it is a question how much good it does in clinical practice It is hard for me to understand how one can produce a sustained physiologic effect in the bowel without at the same time making the mouth dry and the eyes weak

Anticonstipation Diets —The usual diet prescribed is one that contains as much indigestible material as possible The patient is told to eat heartily of green vegetables salads, fruits, bran muffins, whole wheat bread prunes and figs.

When such a rough diet works satisfactorily, the patient is happy, and I can see no reason for asking him to change his habits My only objection to rough diets is that they sometimes produce flatulence, abdominal distress and malnutrition For this reason, I think the physician, when he prescribes a rough anticonstipation diet, should always warn the patient that if he should later begin to suffer with intestinal unrest, he should remember that he is eating avowedly indigestible material, and for a time he should go back to a smooth diet to see what happens Another difficulty with even the bulkiest diet is that although it may work beautifully for a month or so, in some patients it soon tends to lose its efficacy, in other words, the bowel becomes accustomed to it In these cases the patient may do better if, from time to time, he goes back to a smooth diet

Fortunately when a constipated person has a weak or handicapped digestive tract which will not tolerate the roughest foods, the physician can still add bulk to the diet without producing much irritation He can prescribe agar or other hygroscopic substances such as normacol psyllium seeds prune pulp or the finely ground pure cellulose which is supplied in Heinz rice flakes Particularly when the patient is thin one of the best additions to the diet is fat, in some cases it works like a charm It is almost certainly his large fat ration which keeps the Eskimo from suffering with constipation

Even when the smoothest most finely ground and least irritating forms of indigestible food are added to the diet, experience teaches me that their presence can embarrass digestion in some sensitive persons and can so add to the burden of the bowel and so stimulate peristalsis that the patient will feel discomfort

One of the commonest substances used today for the relief of constipation is mineral oil with or without the addition of agar or a salt of magnesium There is no question that the action of these mixtures is highly satisfactory to thousands of persons but I never cease wondering how these people digest or absorb their food with so much indigestible oil mixed in with it Perhaps, when distributed over the long small bowel there isn't enough oil to do much harm and perhaps it does not tend to coat particles of food So far as I know it rarely causes malnutrition Occasionally it seems to cause indigestion, and often its use has to be stopped because it begins to pass through the bowel unmixed with the feces

My main objection to expensive colon washing by quacks physicians and nurses is that I doubt if a course of such treatments can ever cure anything The cleansing of the colon can doubtless make some persons feel much better at the time but if the effects are not lasting the end of the course must find the patient in exactly the same condition as he was at the beginning If he must then begin to take the enemas himself he might just as well have started earlier and saved his money

Some persons believe that massage will relieve constipation It is possible that the stimuli thus given to nerve ending in skin and bowel will start up peristalsis but I am sure from many experiments performed under the fluoroscope that one cannot through manipulation of the bowel push fecal masses from one segment to another

Operative Interference — It is possible that in the future more patients with severe and inveterate constipation will be operated on The work of Royle and of Adson and Learmonth has shown that the severing of the sympathetic nerves controlling the internal sphincter of the anus will sometimes bring relief to children with Hirschsprung s disease Unfortunately the results obtained with this operation in the case of a few constipated women were not so good It is possible that some other types of operation on the sphincters or on the nerves supplying them will ultimately be devised The difficulty is that after any operation the constipated bowel is so likely to fall back into its old habits

On rare occasions one sees a patient who years ago submitted to a right colectomy and who still is satisfied with the result The great difficulty that I see in the use of all such operations arises from the fact that it is hard to find a patient with the severest form of constipation who is not so neurotic that he or she is a poor subject for any operation and particularly for one in which the work must be somewhat experimental For such work one needs an intelligent well balanced cooperative friendly type of patient one who if he is cured will recognize the fact and if he is not cured will not bring suit for damage To show how difficult it is to find such a person I need only say that after five years of search I have not found one whom I cared to urge into an operation for the relief of constipation Occasionally I will find one who looks like a promising candidate but when I keep him around for a week or two long enough to really make his acquaintance I change my mind

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up in the rectum, it cannot get past the valves of Houston A short hard rubber tip should therefore be used It is needless to lie down while taking an enema If one runs in a liter and a half of water it must go somewhere and even if the person is seated, it must reach the right half of the colon Finally, it is foolish to try to hold the water because this only accustoms the colon to the distension and as a result the enema is not easily voided Another common reason for the failure of the water to return is probably that the patient, fearing to run in more than a pint at a time, fails to stimulate the colon to contraction

The third common objection to enemas is that they are too irritating So much spasm is produced in the bowel that it is hard to run the water in and it is hard to get it out The patient has to keep returning to the toilet every few minutes for perhaps several hours, each time getting rid of only a little water and some mucus In this case, and especially in the case of the person with an exceedingly sensitive colonic mucosa, the physician can often give wonderful relief by prescribing an enema of warm physiologic saline solution. In order to sell the idea I often say to a patient, "Your colonic mucosa appears to be almost as sensitive as the conjunctiva of your eye Tears do not hurt your eye so they cannot hurt your colon What are tears? They are drops of physiologic saline solution

In most of the patients with an extremely sensitive colon and an indigestion due to constipation, wonderful relief can be obtained when the fecal plug is washed out every day or every other day with a liter and a half of saline solution A rounded tablespoonful of salt should be dissolved in the bag of warm water The warmth will tend to relax the colon, and this will make it easier for the fluid to run in The enema should be taken with the patient seated on the toilet and the bag suspended about a foot above the shoulder

There is a type of oil enema that can be retained all night On retiring, the patient runs from 90 to 180 c c (3 to 6 ounces) of warm olive oil into the rectum with the help of a large catheter and a small funnel In some cases this procedure works and a normal stool is secured in the morning

There are a number of men, most of them outside the medical profession, who for a consideration love to wash out the bowels of patients with a complicated apparatus and a tube which is supposed to be passed into the cecum They swear that they can cure all sorts of diseases but on talking to some of their ex patients I have not been able to satisfy myself that the results they obtain are much better than those that can be secured at home with a simple enema bag by the patient himself I have satisfied myself in the case of a few patients with the colon filled with barium that an ordinary enema can clean out the large bowel from one end to the other In most cases I doubt if it is desirable to clean out more than the left half of the colon because I believe it is physiologic for the right half to retain some material for two or more days

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W C A.

Intestinal Sensitiveness to Foods

It seems probable that many of the patients who now pass through the hands of gastro enterologists without receiving a definite diagnosis are suffering from a sensitiveness to one or more foods It is probably an exceptional person who can eat everything with impunity nearly everyone seems to have some article of diet which he or she finds more or less distressing Often of course the knowledge is not definite The commonest story is that years ago, perhaps after a picnic, there was a violent upset of digestion with nausea vomiting cramps and diarrhea the blame was put, let us say on some pimiento cheese sandwiches, and the patient never touched pimiento cheese again Obviously he doesn t know anything definite, the cheese may have been innocent and if he were to experiment with it again he might find that he could eat all he wanted of it Even if it were at fault years ago it might not cause trouble now One can suddenly acquire sensitiveness to a food and later lose it.

Not infrequently, food is irritating because it is infected with harmful bacteria The more they study this problem the less inclined bacteriologists are to blame acute digestive upsets on ptomaines , and the more inclined they are to place the responsibility on living organisms If the physician will study the blood of patients who have suffered with vomiting and diarrhea after eating at a picnic or in a dirty restaurant, he will occasionally find that there is a decided ability to agglutinate organisms of the typhoid dysentery or enteritidis groups In other cases, it is possible that the meat eaten had become contaminated with toxins of bacteria growing in the intestine of the animal Thus I suspect that some persons are sensitive to the meat of an occasional chicken because the bird was not drawn soon enough after death Cases have been reported also in which severe poisoning was produced by the eating of food contaminated by the feces of mice whose intestines were infected with bacteria of the typhoid group

Many persons know that they must not eat certain foods Often the idiosyncrasy was present in infancy or childhood, and the ingestion of milk or eggs produced eczema or nausea or colic flatulence biliousness ' and diarrhea. Strawberries often cause hives and shellfish may cause vomiting and purging

Cabbage apples onions radishes, chocolate, green peppers, condiments and melons are other common causes of gaseous distress, regurgitation, or soreness and burning in the bowel

The fact that a patient has discovered his sensitiveness to some foods should always make the physician wonder if careful investigation might not reveal other articles of diet which are irritant and perhaps responsible for mo t of the symptoms complained of What makes the search for these offending foods difficult is that so often there are several of them and they are among those that are being eaten every day Another difficulty is that small amounts of these foods may be eate with impunity, or a food may be eaten for one or two days in succession but not for three days Because of these difficulties the discovery of the troublemakers may require a considerable amount of detective work and much of it requires intelligent and pertinacious cooperation on the part of the patient

It is the custom nowadays to speak of most of these disturbances as allergic in origin but I doubt if this i justifiable It seems to me that the term allergic should be reserved for those cases in which the patient or his imme diate relatives suffer from other manifestations of allergy such as hay fever asthma and urticaria and particularly for those cases in which the re ponse to the injurious food is sudden and violent and associated with signs of spasm in smooth muscle in various parts of the body Thus there are persons who within a few minutes after eating a minute amount of some shellfish find them selves ga ping for breath and swelling here and there with the wheals of giant urticaria In other cases there will be severe headache violent abdominal cramps marked irritability of the bladder and pains throughout the joints

In most cases it seems to me more probable that the offending food acts not allergically, but by direct irritation of the bowel Substances such as pepper mustard and other condiments may irritate the mucous membrane and the nerve endings in it just as they irritate the nerve endings in the mouth As a result the patient feels as if the abdomen were on fire or he suffers with colicky pains due to incoordinated contractions of the bowel Flatulence may be due to disturbances in the circulation of the gut which interfere with the normal transportation of intestinal gases to the lung

There are a number of foods particularly melons which contain some chemical substance that tends to reverse the direction of peristalsis in the digestive tract and to produce regurgitation Fats slow the emptying of the stomach and also tend to produce reverse peristalsis with nausea and regurgita tion Other foods such as onions may acquire a bad reputation simply because their essential oil happens to become dissolved in the fat which normally floats on the top of the liquid contents in the tomach and as a result the patient keeps tasting it whenever he belches or regurgitates

Foods such as cabbage, cauliflower, and peanuts appear to contain some chemical substance which is irritating to the digestive tract of many persons Other foods such as raw apples, and many of the other raw fruits, salads and leafy vegetables are hard to digest probably because they contain so much cellulose and other woody material which the intestine cannot handle successfully Unfortunately the digestive tract does not appear to contain any ferment for the splitting of cellulose

The physician will be the more inclined to search for offending articles of diet if the patient or members of his family tend to suffer with hives, hay fever or asthma He will be suspicious also when symptoms are largely those of a sensitive colon, that is, soreness and burning in the lower part of the abdomen with flatulence and the passage of large amounts of mucus in the stools Other suspicious symptoms are headache slight diarrhea, nausea, irritation of the bladder and pains in the joints

Methods for Discovering the Foods that are Causing Indigestion

Skin Tests —The skin tests, which are often helpful in the discovery of the causes of hay fever and asthma, are seldom of value in revealing the foods that the patient should not eat Some specialists in allergy report the finding of positive skin reactions in some of these cases, but then the difficulty is that the patient commonly responds to certain foods one day and to others on another day Some investigators try to improve matters by repurifying the antigens used but this does not seem to be a promising line of endeavor in view of the fact that in many cases the offending substance is probably not a protein Certainly I can see no reason why we should always assume that it is a protein or that the more we purify it the better skin reactions we will get Perhaps we would get better skin reactions if we were to use powdered whole substance and not the purest proteins that we can extract Actually in most cases, it does not pay to spend the patient s time and money on skin tests

The Notebook Method —When the upsets in digestion or the attacks of migraine, mucous colitis, or urticaria come at intervals of weeks or months, the cause may perhaps be found if the patient will make each time a written record of all the unusual foods not eaten every day, that were consumed in the previous twenty four hours After a while it may be seen that some one article of diet was taken before every attack or it may be found that an unusually large amount of some commonly used food was eaten In keeping such a record, note must be made also of unusual fatigue or emotion, of the presence of constipation or migrainous headaches or of eating when distraught or angry or in a hurry, or when mentally preoccupied The more I practice in the field of gastro-

enterology the more impressed I am by the fact that often it is not so important what the patient eats as how he feels while he is eating it

Not infrequently it will be discovered also that indigestion which at first appeared to be due to the eating of one or more foods was really only a prodromal symptom of an oncoming cold In other cases of course it will be found that the upset which was ascribed to the taking of some food was really but an episode in the course of an organic disease of the digestive tract such a cholecystitis duodenal ulcer chronic appendicitis or carcinoma

A variation of this notebook method consists in having the patient eat for a few days large amounts of some food If nothing unusual happens one can be fairly sure that this food can be eaten with impunity

ELIMINATION DIET FOR DIAGNOSIS AND TREATMENT OF FOOD ALLERGY

	Diet No 1	*Diet No 2*	*Diet No 3*	*Diet No 4*
Cereal	Rice	Corn Tapioca	Rice Rye	Milk alone for the test period 2 to 3 quarts a day
Bread	Rice biscuit	Corn pone	Rye rice	
Meat or fish	Lamb	Bacon Chicken	Beef	
Vegetables	Lettuce Spinach Carrots	Squash Asparagus Peas Artichokes	Tomatoes Beets String beans	
Fruits and jams and fruit drinks	Lemon Pears Peache	Pineapple Apricot Prunes	Grapefruit Pears Peaches	
Miscellaneous	Sugar Olive oil Salt Gelatin Syrup made from cane sugar flavored with maple Olives (unstuffed)	Sugar Mazola oil Salt Karo corn syrup	Sugar Wesson oil Salt Gelatin Syrup made from sugar flavored with maple	

The Elimination Diet — When the distress complained of is present after every meal or when it comes every few days the problem of finding the offending food or foods must be simplified by reducing the number of possibilities The simplest method would be to have the patient fast for a week or more

Foods such as cabbage, cauliflower, and peanuts appear to contain some chemical substance which is irritating to the digestive tract of many persons Other foods such as raw apples, and many of the other raw fruits, salads and leafy vegetables are hard to digest probably because they contain so much cellulose and other woody material which the intestine cannot handle successfully Unfortunately the digestive tract does not appear to contain any ferment for the splitting of cellulose

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The patient may next test eggs to see if he can eat one or two or as many as he likes Always when there is an upset or when there is doubt the experiment must be repeated several times

Some of the persons who know that they must not eat milk or eggs in undisguised form probably suffer from indigestion because they do not stop to think that they are taking considerable quantities of these foods mixed in with others Similarly, a man who is highly sensitive to corn may not realize that he is being harmed when he eats a sauce or a pudding containing corn starch or when he eats candy or some syrup containing corn sugar or when he takes mayonnaise from corn oil or even when he eats a piece of fish fried in such oil It must be admitted however that some persons who feel sure that they cannot take some particular food undisguised, eat it with impunity when it is hidden away in mixtures

When symptoms of indigestion continue during the time in which the patient adheres to the narrow diet of lamb and rice the problem becomes more difficult In cases of migraine Rowe believed it is advisable to continue with the experiment for ten days so as to give time for all the wheat or other offending food to work out of the system Ordinarily when the symptoms do not clear up after three days of dieting it is to be feared that at least one of the foods eaten is causing trouble and a search must be made for it Thus the lamb may be given up and perhaps beef or chicken substituted The other possibility of course is that the symptoms complained of are not due to any particular food and therefore cannot be relieved by any diet

In many cases unfortunately the physician soon discovers that he is dealing with an extremely fussy psychopathic unreliable or scatter brained person who will not follow in tructions who will cheat and who is hardly worth trying to help These people come complaining to Heaven of their pains and aches they have travelled a thousand miles and more to find relief they are willing and perhaps eager to submit to an operation but to go without their coffee for three days oh no that would be too much!

In some cases in which the patient is fairly sure that he can tolerate milk, his elimination diet may consist of two or three quarts of it a day and nothing else Sometimes fermented milk is easier to take than sweet milk If this diet brings comfort other foods can then be added one by one

In the search for the offending articles of food it is helpful to remember that the commonest ones complained of by a series of one hundred patients interrogated by me were in the order of frequency cabbage apples tomato milk chocolate onions lettuce coffee strawberries eggs meat cucumbers fats and greasy foods sweets radishes cheese cauliflower spices peanuts corn cantaloupe peppers prunes, oranges salmon sweet potato sour foods peas pickles and pork

If then the distress were to continue, the physician would know that food was not the cause or at least not the principal one If the distress were to cease, then various foods could be tested one by one and the diet could finally be made up of those substances that did not give distress Since many patients are undernourished when first seen and in no condition to stand a fast and since most of them would object to such deprivation, the next best thing is to give a few foods chosen from the list of those that seldom appear to give trouble

The preceeding table is taken from Rowe s book on food allergy If the symptoms do not clear up on the first diet, the patient may try another

I have found a useful elimination diet to consist of nothing but lamb rice, butter sugar, lemon jello and canned pears For breakfast the patient may take a lamb chop with puffed rice or Heinz rice flakes or steamed rice with butter and sugar No sauce or pepper or gravy should be used on the meat The only drink allowed is water For luncheon the patient may eat a chop or a piece of roast lamb with rice and dessert Cream must not be used Dinner will be the same as luncheon Obviously soda fountain drinks candy and even chewing gum must not be touched Every added substance put into the mouth complicates the problem

During the progress of these tests some constipation should be expected and disregarded because the diet is so free from residue If the patient feels he must have a bowel movement every day, he may take an enema of physiologic saline solution During the period of observation, agar, bran, paraffin oil and all other laxative substances must not be used

If on this narrow diet the symptoms promptly disappear, the problem is almost solved because all that remains to be done is to try one additional food at a time, testing it for three or four days and keeping a record of what happens Thus the patient may begin by experimenting with a quart of milk a day If this causes nausea gas or biliousness, its use should be stopped and a record made of the bad effects produced Next, bread and other wheat products may be tried Let us say that the patient is comfortable for a few days and then gets an attack of indigestion or migraine He should then stop eating wheat and go back on the basic diet for several days so as to allow time for the elimination of the harmful substance from the body

He may then again try taking a small amount of milk or cream a day If this distresses him, he can be fairly sure that he must not touch milk If on the other hand he finds that he is only moderately sensitive to this food, he can take a small amount every day He may find also that he can take small amounts of milk when it is incorporated in puddings, soups, creamed sauces, ice cream, or custards He will have to experiment also with different kinds of cheese Some persons are so highly sensitive to milk that they cannot use much butter

the eating of harmful foods but my experience makes me very doubtful of this So far as I can learn only a small percentage of migrainous persons can be cured by a change in diet.

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W C A

Failure of Rotation of the Colon

According to Carey the embryonic cells which eventually form the colon tend to grow in a spiral In so doing they put a twist in the bowel which causes it to loop over just as a piece of rope would under similar compulsion This loop forms the transverse colon and cecum During the rotation of the colon the progress of the cecum may be arrested anywhere along its journey across the upper part of the abdomen to the region of the right kidney and then caudad to the right iliac fossa The mesocolon is formed by the fusion of the peritoneal coat of the bowel with that of the posterior wall of the abdomen This fusion may be partial or incomplete

In the most striking cases of failure of rotation the entire colon will be found on the left side of the abdomen Occasionally these abnormal positions of viscera give rise to serious trouble and at other times they make diagnosis difficult Thus Weiss has reported a case of appendicular abscess in which the cecum was found adjacent to the splenic flexure of the colon Crove reported a case in which the colon lay entirely in the left side of the abdomen with the cecum in the usual position of the sigmoid loop and an anomalous attachment of part of the colon to the duodenum and jejunum This was the cause of a life long diarrhea because the trouble disappeared as soon as the cecum was pulled over where it belonged and fixed in the right side of the abdomen

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J A B
W C A

According to some students of this subject wheat should head the list, but as yet I have not been able to satisfy myself of this Certainly if wheat is the commonest offender, patients rarely discover this fact for themselves

It would be well if every man who intends to specialize in this field would begin with so large a clinical experience that he could ever afterward "keep his feet on the ground" and could keep from getting too excited over those occasional cases in which his study of the patient's dietary idiosyncrasies results in the working of a miracle It is only the physician with a wide clinical experience who, under these circumstances, remains calm and remembers that even when patients obtain prompt relief on an elimination diet the good result is not always permanent and due, as at first appears, to abstinence from certain foods Too often patient and physician will be disappointed later to find that the improvement was probably due to rest from work or escape from worry and annoyance at home, or to the securing of better sleep, to the elimination of roughage from the diet or to a lessening of the amount of work demanded of the digestive tract Even when spectacular relief was obtained by removing one or more articles from the diet, the patient later can develop a sensitiveness to other things or he can "spring the trap" with other triggers such as worry, anger, or infection It is well to remember the adage that "once an allergic always an allergic" because there is much truth in it

It is advisable therefore, that after a few weeks or months the patient experiment again with the foods that appeared to be harmful, because often it will be found that he has regained the ability to eat some or all of them Many times foods are condemned unjustly and on insufficient evidence often they should be given another chance and always the patient should try to avoid that common tendency of dyspeptics to give up one article of diet after another until few are left and health is impaired

This whole problem of sensitiveness to foods is intimately bound up with the problem of so-called mucous colitis I have seen a number of patients with typical attacks of mucous colitis which could be brought on by the eating of harmful foods The interesting point is that, when these persons knew what foods to avoid, they still suffered occasionally with attacks of mucous colitis, attacks which were brought on by worry, fatigue, or a tantrum the taking of a laxative or the catching of a cold It appears then that food sensitiveness, although perhaps a common cause of mucous colitis, is not the only one

It is wise in all puzzling cases of "idiopathic" diarrhea to put the patient on an elimination diet because otherwise the physician will occasionally be humiliated later to learn that the trouble which had been so resistant to all of his strenuous treatments was instantly cured by the removal of some article from the diet

There are some enthusiasts who claim that all cases of migraine are due to

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J A B
W C A



FIG 10 Melanosis coli

MELANOSIS COLI

It is always a startling sight to see at the necropsy table a black colon with the pigmentation stopping abruptly at the ileocecal sphincter (Fig 10) The

Abnormal Position and Mobility of the Colon and Cecum

The careful work of Moody with more than a thousand healthy university students should convince anyone that a low lying stomach or colon is so common and so normal that of itself it can hardly be looked on as a sign of a disease The only loop hole left for those who continue to argue that coloptosis or cecum mobile is a disease is that in some delicate persons the ptosis and mobility might cause symptoms According to these writers, the slight physical abnormality is responsible for fecal stasis, and this produces indigestion, flatulence, lassitude and mental and physical inertia

The symptoms are supposed to be curable by operations in which the cecum and ascending colon are fastened to the abdominal wall According to Carlslaw 13 of 242 patients, who were operated on in this way, were satisfied with the result Among signs of improvement was a return of appetite, and relief from flatulence constipation and bilious attacks ' The difficulty with most such analyses is that the patients are not studied long enough too often there is good relief for a few months, and then the old troubles return or new ones develop

In addition to the abnormally mobile and low lying cecum the surgeon often finds bands of peritoneum usually congenital and developmental in nature, which are supposed to be factors in producing symptoms Among these are the lower ileal or Lane s membrane, the pericecal membrane or Jackson s veil the mesosigmoid membranes the mesocolic jejunal (Mayo) membrane, and the right and left intercolic membranes

As every clinician of experience knows, the great difficulty with most of the patients on whom cecopexy is done is that they are usually neurotic, hypersensitive and constitutionally inadequate They cannot stand the stress of modern life, and there is no way yet known in which they can be made over Years ago Sistrunk at the Mayo Clinic operated on a number of such patients and seemed at first to get good results in some cases but in many, the ultimate outcome was such as to discourage him from making further efforts along this line We doubt therefore if the mobility of the cecum or the ptosis of the colon by themselves were responsible for the illness which the patients complained about

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and roentgen ray films will not show more than the usual amount of scarring. In some of the girls there is more than the usual rise in temperature at the time of menstruation and sometimes the question of tuberculous salpingitis cannot be disposed of without the help of an exploratory laparotomy.

Physical examination generally shows a thin nervous more or less prostrated young woman with a temperature around 100° F, a tender abdomen and usually a right rectus scar the reminder of a useless appendectomy. Roentgen ray examination of the stomach, gallbladder and colon will not show anything wrong. Occasionally calcined lymph nodes will be seen in the films made of the abdomen. Now that the medical profession is cognizant of the frequency with which infection with Brucella abortus and Bacillus tularense takes place and is supplied with diagnostic tests for the recognition of such infections, it may be found that these organisms are responsible for some of the cases of mesenteric lymphadenitis.

If the abdomen of such a patient is explored the surgeon will find scattered throughout the mesentery enlarged lymph nodes. If he removes one or more of these the pathologist will usually report inflammation of unknown origin and cultures will fail to show any growth. The impression gained will be that the patient is suffering with some chronic low grade infection. Hodgkin's disease can easily be excluded because in the disease under discussion the nodes remain discrete.

Treatment

The treatment must be largely that of tuberculosis and must consist of rest in bed, heliotherapy and attempts at overfeeding. The improvement of nutrition is difficult because of the marked anorexia and the attacks of vomiting. The diet should be as smooth and as rich as possible. Sedatives are often needed, particularly at night.

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IRRITABLE COLON OR MUCOUS COLITIS

The term mucous colitis is inappropriate because the symptoms do not seem to be associated with or due to an actual inflammation of any of the

color is sometimes lighter and may vary from yellow to grayish brown and finally to tarry black As the condition appears never to be associated with any ailment more serious than constipation, it has little clinical significance It was adequately described by Virchow in 1847 and studied more carefully by Pick in 1911

Colonic pigment that can be seen with the naked eye is rarely met with in persons younger than forty years of age, but with the aid of the microscope it has been detected in boys and girls dying about the age of puberty From studies made it seems probable that some pigment could be found in the colonic mucosa in about a third of all human beings who live past middle life

According to Pick, the coloring matter is to be found in the tunica propria of the mucosa and not in the epithelium It is located in large mononucleated fixed cells which appear to have their origin in the muscularis mucosa Heuschen and Berstrand (1913) found it in wandering cells and Dalldorf (19) found it also in fixed cells It never enters the pericolic lymph nodes, and only occasionally has it been found in the terminal portion of the ileum

All that is known about the pigment is that it is related to melanin (Pick and Brahn) It is not a compound of iron it is not a bile pigment it is insoluble in acid and alkali but antiformin and some acids will bleach it

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J A B

Chronic Mesenteric Lymphadenitis

There is a rare disease in which patients complain of diffuse abdominal pain, anorexia, slight fever flatulence bloating, occasional diarrhea, marked prostration great nervousness occasional attacks of vomiting and decided loss of weight In some cases the patient is more or less bed ridden for several years In some of them a subacute arthritis is associated with the syndrome

In many of these people one can get a history of heavy exposure to tuberculosis in childhood but at the time of examination it is usually impossible to say whether or not they have tuberculosis The lungs will seem to be clear,

who can be made happy by the gift of an impressive Latin name for their symptoms

My impression about the sensitive colon is that it is usually inherited and as one would expect if this be the case it is not a condition that can be cured Instead the victim must learn to live with his or her handicap Once a woman shows marked signs of the disturbance (I dislike calling it a disease) she is likely to suffer with it at intervals for the rest of her days The more fortunate members of the affected families suffer from the typical symptoms only at rare intervals, as when they are going through some severe emotional strain

In most cases the patient is a woman high strung nervous overly sensitive, neurotic, or psychopathic The symptoms usually make their appearance early in life and they tend to disappear with advancing years On a few occasions I have seen the trouble appear in middle life in men who assured me that they had previously enjoyed good health

The women who suffer most with the disturbance often have defective pelvic organs and severe menstrual storms Others give a history of attacks of hay fever or urticaria or asthma, or it may be found that some of the relatives suffer with allergic manifestations An allergic type of response to foods and various irritants is doubtless one of the causes of the spasm in the colon and the excessive secretion of mucous but I am sure that it is not the only one I have seen patients with marked sensitiveness to foods who with the help of an elimination diet were able to discover and identify all the foods to which they were sensitive They then made the interesting observation that occasional attacks of mucous colitis would precede the onset of a cold or follow emotional storms, fatiguing experiences or the taking of a laxative

Symptoms

Constipation is almost always troublesome and is due probably to the spasmodic contraction of the muscle in the walls of the colon Instead of allowing the feces to accumulate in the rectum in long sausage like masses which can be extruded with ease the overly active and sensitive bowel rolls the material into hard pellets which can be passed only with difficulty

In mild cases and between attacks the mucus will be detectable only by suspending the feces in water and floating them over an illuminated ground glass slide During attacks large strings of mucus or even large membranes will be passed Patients will sometimes present the physician with a quart jar full of such material the passage of which has alarmed them greatly Not infrequently after a barium meal enough of the opaque material will adhere to the mucus so that long strings will be visible in the roentgenograms of the bowel

Diarrhea is seldom pre ent, and when it is it may be due either to the

coats of the colon Even when the disease has been exceedingly troublesome for many years my experience is that at operation or necropsy the colon appears to be normal, its walls are not thickened, there is no ulceration of the mucous membrane, and if abnormal cells are found in it they are usually eosinophiles

For these reasons I think it would be well if the medical profession would drop the term mucous colitis, and until a better label is found, use instead the words, irritable colon A better terminology might help the physician to keep clear in his mind the distinction between this functional disturbance and the true inflammations of the bowel It would also tend to reassure neurotic and worrisome patients who now get the idea that they are suffering from a serious organic disease Troublesome the syndrome certainly is, but the only dangerous feature is that some well intentioned surgeon is likely to insist on performing one or more useless operations Aside from this unfortunate sequela the only one I know of is that the patient may become a querulous, colonocentric invalid, one who can talk of little else besides the appearance and consistency of the last stool passed It is now twenty years since I first assumed the care of several women with the severest forms of "mucous colitis", with or without my consent they have each submitted to three or more usually useless, operations on appendix, uterus and gall bladder, and still they suffer occasionally just as they used to do The encouraging point is that with the passage of years their troubles have tended to become better instead of worse, and no one of them has come to any bad end In many cases, therefore, the first and most important step toward helping the patient is taken when the physician tries to reassure her and to get her to stop worrying about the condition and about the passage of mucus

It is unfortunate today that so many roentgenologists and physicians are inclined to make the diagnosis of "colitis" when they see on the roentgen ray film signs of a highly irritable spastically contracted colon with unusually deep haustra In such cases sigmoidoscopic examination usually fails to show any ulceration of the mucous membrane, the patient is constipated there has never been any complaint of diarrhea and to my way of thinking, the diagnosis of colitis is not only wrong and unjustified but it is harmful because it works injury to the mind of the sufferer

It seems to me that the term colitis should be reserved for those cases in which one can demonstrate inflammation or ulceration of the colon The advance of scientific knowledge is dependent upon the use in all civilized countries of an exact nomenclature in which the meanings of words are kept distinct and constant, the ending *itis* has come to denote inflammation, and it would seem best, therefore not to apply it to diseases in which inflammation cannot be demonstrated As Munthe points out in his delightful story of San Michele, the term colitis has only too commonly been used as a placebo for neurotic women

feces are present in the rectum and the sufferer goes to the toilet every hour or so only to pass a few small pellets of feces or a little mucus or gas

So far as I have been able to learn direct inspection of the rectal and sigmoidal mucosa does not show any characteristic abnormality As I have already stated, the roentgenogram may show deep haustration or some crinkling of the outline in the descending portion of the colon but the less one talks of these things to the patient the better Similarly the experienced and conscientious physician will say nothing about the perfectly normal ptoses kinks and redundancies that he will find in every other roentgenogram studied

The appearance of sticky greasy, gluey ice cream like and peculiarly smelling stools in some attacks of mucous colitis makes me suspect the presence of some abnormality in the secretion of the pancreas or in the absorptive power of the small bowel These stools sometimes cause much of that burning in the anal canal which is so trying to the patient I have often wondered also if the soreness of the colon might not at times be due to the excretion into it of some irritant substance previously absorbed by the small bowel or else formed in the body What makes me think of this is the fact that there are a number of substances that are known to be excreted through the colonic mucous membrane Unfortunately the careful chemical studies which ought to be made of the stools of these patients when they feel toxic and sleepy and miserable have not yet been undertaken and as a result a rich and clinically most important field for research still lies fallow

Treatment

The most essential part of the treatment must consist first of a good frank talk with the patient in which an effort is made to dispel acquired fears and to put in their place exact information as to the nature of the problem The sufferer must be made to see that the trouble is not a serious disease that requires an operation or a strenuous course of colonic washing He or she must give up the hope of being cured in the sense that there will never be any tendency to recurrence of symptoms Once a sensitive colon always a sensitive colon or at least until age brings a lowering of general bodily irritability

In many cases the next thing to do is to relieve constipation without at the same time irritating the bowel Often all the physician has to do with these patients is to take from them the bran spinach and other cellulose rich articles of diet with which they have been stuffing themselves It appears logical to expect that a highly sensitive bowel should be least injured and irritated by a smooth and fairly concentrated diet and in many cases the giving of a smooth diet does bring relief In other cases in which the emotional factors are the most important ones the character of the diet is probably unimportant

over activity of the bowel, to irritation from some food, or to inflammation produced by feces which stagnate and decompose in the cecum Flatulence is a common symptom Pain usually is complained of, and in the worst cases it is severe enough to be confused with that of appendicitis cholecystitis, renal colic or intestinal obstruction The diagnosis is made most easily when the pain comes in attacks which are associated with the passage of membranes of coagulated mucus There is no doubt that many needless operations are performed on account of such pain

The physician will think particularly of mucous colitis when, in a nervous woman the pain is widespread through the lower abdomen, and when it follows the course of a markedly contracted and highly sensitive colon The pain of ulcer cholecystitis and even of acute appendicitis is generally in the epigastrium or upper part of the abdomen Indicative of the colonic origin of some abdominal pains will be the fact that they are relieved by the taking of an enema or by the passage of flatus or feces or mucus It is helpful also to find that the attacks come usually when the patient is fatigued or worried or angry or mentally upset over a love affair, a family quarrel, or a business loss I know a very nervous Jewess with an exceedingly sensitive colon in whom for years the condition of the bowel followed the ups and downs in the precarious health of a frail and only child Every time he went to bed with measles, mumps, or chicken pox his mother was prostrated with a severe attack of ' mucous colitis

In the worst cases an attack may last a week or ten days during which time the patient is confined to bed with colicky pains, great soreness of the abdomen and perhaps nausea, vomiting and headache Sometimes the attack is associated with a stormy and painful menstrual period There is rarely much febrile reaction In bad cases the abdomen is scarred and discolored from the application of countless hot water bottles In many cases the patient is of the constitutionally inadequate type, often she is thin, but occasionally I have seen severe attacks in women who were fat

The normal appearance of the colon, the absence of sequelæ and the fact that most of the patients are decidedly hypersensitive and neurotic women, all indicate that the disturbance in the bowel is a functional one and due to some abnormality in the nervous system In some cases of course, it may be due to direct irritation by substances in the food In the worst cases the patient s life is largely ruined by his or her constant preoccupation with the painful or disagreeable sensations that come from the lower part of the bowel There can be no question about the intensity of the suffering of many of these persons, and it is only a strong stoical type of nervous system that can stand without injury the constant stream of unpleasant sensations arising in the colon Day after day the patient feels conscious of the bowel, often there is a feeling that irritant

take a teaspoonful of paregoric This may quiet the bowel sufficiently so that there will be no distress

When there is definite disease in the pelvic organs it may help the colonic condition to have this attended to surgically but one cannot promise a cure In a few cases in which the menstrual storms were exceedingly severe and apparently responsible for the great irritability of the colon I have been driven to induce an early menopause either with radium or a hysterectomy There has usually been some improvement but never complete or permanent relief In some cases in which mucous colitis is associated with cholecystitis cholelithiasis and chronic appendicitis operation may help the colonic syndrome somewhat, but in a number of instances I have found that the sensitiveness of the bowel has not been lowered

It seems probable that at times attacks of mucous colitis are due to or associated with changes in the flora of the bowel but such changes are hard to detect even when an expert bacteriologist makes extensive studies of the stools with aerobic anaerobic and fermentation media As yet an efficient colonic antiseptic has not been discovered and the clinical value of acidophilus milk or of the recently introduced soricin (sodium ricinoleate) which can detoxify bacteria is still doubtful

W C A

Syphilis of the Intestine and Rectal Crises of Tabes

The rarity of syphilis of the intestine is shown by the figures of Frankel who in the reports of 19 000 necropsies found only two in which there was mention of the disease In Oberdorfer s 24 proved cases of intestinal syphilis there were 16 in which the disease was in the small bowel usually in the jejunum in 4 it was in the large intestine and in 1 it was confined to the ileocecal region

A catarrhal enteritis has been described as occurring in the secondary stage of syphilis It usually produces some abdominal distress and a mild or moderately severe diarrhea Unfortunately in a given case it is not possible to prove that the cause of the symptoms is syphilis This can only be surmised if relief follows promptly on antisyphilitic treatment It is possible that in some reported cases in which relief of diarrhea followed the taking of arsphenamine the real cause may have been an unrecognized amebiasis which was cured by the drug

Intestinal lesions are rare in cases of late or tertiary syphilis When they do occur they consist of gummas ulcers and strictures The only symptoms usually produced by gummatous lesions are those of obstruction A syphilitic ulcer may perforate and give rise to peritonitis or it may become adherent to neighboring viscera (Riggs)

In years past most clinicians tended to follow von Noorden's advice in treating these patients with a rough anti constipation diet, but I think the present tendency is to use a smooth diet and to relieve constipation with the less irritating bulk producers such as agar, normacol (Schering), prune pulp mineral oil or the finely ground cellulose in Heinz rice flakes A still better way of relieving constipation and intestinal irritability in many of these cases is to wash the bowel out with an enema of warm physiologic saline solution. Such an enema relieves spasm, it removes feces, and it removes irritant chemical substances

Several women with a very sensitive colon have told me that of the laxatives, the least irritating for them seems to be calcined magnesia Some do well with oil enemas At bed time a few ounces of warmed salad oil are run into the rectum with the help of a small rubber tube attached to a funnel This oil is retained until the morning

Medicated enemas and expensive colonic flushings with elaborate apparatus may be remunerative to the physician and occasionally much appreciated by the patient, but ordinarily they are of little value because their effects are so transient and the efforts made are so sadly misdirected The trouble is not all in the bowel but most of it is in the unruly emotions and hyper ensitive nervous system The mucus is an unimportant by product, and no amount of washing out of this substance is going to work a permanent cure

The time when an enema is most useful is often in the evening when the cleansing of the colon may result in a more restful night s leep than would otherwise be had

In all cases in which relief is not immediately obtained with a smooth diet, rest and sedatives, every effort should be made to search for offending foods The technic for this has been outlined in the section on intestinal sensitiveness to foods As a rule all condiments and particularly pepper and mustard should be avoided In many cases it is helpful to give sedatives such as bromural, barbital luminal and adalin

Many physicians rely on the use of belladonna, but this drug often causes discomfort in the mouth and eyes and its effects on the bowel are but transient I have never been able to satisfy myself of its value In some cases an occasional dose of codein or dihydromorphione hydrochloride (dilaudid, Bilhuber) or camphorated tincture of opium are helpful Our experience is that they are not likely to produce habituation but naturally their use must be watched and controlled

Sometimes the most trying feature of the disease is the tendency of the bowel to fill with gas and to demand emptying as soon as the victim sits down at a friend s dinner or gets trapped at some public function The resulting misery can often be avoided if shortly before leaving home, the patient will

as if she were being drawn like a chicken Proctoscopic and roentgenologic examinations must always be made to rule out the presence of a local lesion such as a carcinoma Highly characteristic is the way in which the attacks suddenly come and go

Treatment is the same as that for late syphilis elsewhere in the body but unfortunately little can be hoped from it the damage is done and nerves cannot be rebuilt Dihydromorphinone hydrochloride (dilaudid Bilhuber) may be helpful in controlling the pain The effective dose is small and in our experience there is little if any tendency to habituation (For contrary opinion see Eddy Jour Am Med Assoc 1933 C 1032 The Editor) Nerve root section may have to be considered in the more severe cases Unfortunately it often fails to help because the lesion is mainly in the cord

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P W B
W C A

Unusual Granulomas of the Intestine

Every surgeon of large experience can remember having seen a few cases in which on operating for intestinal obstruction or because of a clinical picture strongly suggesting the presence of acute appendicitis or carcinoma of the colon he found a strange granulomatous lesion the origin of which was none too clear even to the pathologist In this article I shall follow the classification of Ginzburg Oppenheimer and Crohn who have described fifty two cases of this type of disease They observed

I Peri intestinal granulomas secondary to sealed-off perforations of the bowel perforations due commonly to fish bones or tooth picks

II Granulomas secondary to vascular disturbances produced by a too prolonged pinching of the gut in a hernial ring In these cases the mucous membrane apparently sloughs and considerable injury is done to the blood vessels in the injured segment As a result the wall becomes thickened with inflammatory tissue and the lumen is much narrowed

III A form of localized hypertrophic and ulcerative stenosis of the termi

It was formerly thought that most of the strictures of the rectum are syphilitic in origin, but studies made at the Mayo Clinic during the last few years indicate that this is not true, at least in the United States of America In this country syphilis of the rectum is a rare disease

Diagnosis

The diagnosis is uncertain and difficult It is fairly easy to say that the patient has syphilis but one cannot prove that the intestinal troubles are syphilitic until one can demonstrate the Treponema pallidum in the tissues Granting that a rectal stricture has been found in a syphilitic patient, the immediate problem is to exclude other causes for the lesion If it were due to chronic ulcerative colitis or amebic dysentery, one would expect to find signs of ulceration in the mucous membrane of the rectum and the sigmoid loop Furthermore diplostreptococci or amebæ might be found in the scrapings from the floor of the ulcers There are some rectal strictures which are due to trauma with secondary infection or to gonorrhea, but in such cases the history of onset should throw light on the nature of the cause

Treatment

Gummatous lesions which produce obstruction must be excised Antisyphilitic treatment should always be given but there will be little reason to hope that it alone can relieve the mechanical narrowing of the lumen of the bowel That occasionally it can do so was shown once in a patient at the Mayo Clinic in whom an obstructing lesion of the colon, which had been demonstrated roentgenologically melted away after the giving of salvarsan

With strictures in the rectum, a combination of anti syphilitic treatment and rectal dilation may bring about sufficient improvement so that nothing further is necessary If however after a fair trial of such treatment, the lumen of the rectum remains too narrow for comfort, a temporary or possibly a permanent colostomy will have to be made

Rectal Crises of Tabes

Rectal crises represent a rare complication of late syphilis Stokes found in several large series of reported cases that from 10 to 22 per cent of the patients suffered with crises In most of them the pain was in the stomach, in others it was in the larynx, and in the fewest it was in the rectum Rectal crises are characterized by severe rectal tenesmus associated at times with the discharge of a little mucus or feces A patient once seen by one of us said that she felt

granulomata of the intestine Trans Am Gastro Enterol Assoc 1932 XXXV, 241

W C A

Solitary Ulcers of the Colon

Occasionally at operation or necropsy the surgeon or the pathologist will find in the colon one or more large ulcers the cause of which is as yet but poorly understood In some cases they have been thought to be due to pressure necrosis from fecal masses and in others there may have been infection of some kind The ulcers which are met with in cases of uremia lesions of the spinal cord multiple neuritis and leukemia will be excluded from the present discussion Those which are described here are usually punched out in appearance they vary from 1 to 8 cm in diameter and if they are ovoid in shape the long diameter is usually parallel with the longitudinal axis of the bowel

Barron, who has collected from the literature reports of 53 cases found that 15 were in the cecum 12 in the ascending colon 3 in the hepatic flexure 5 in the splenic flexure 2 in the descending colon 11 in the sigmoid loop and 4 in the rectum In one case the ulcers were in both the cecum and the ascending colon In 37 of the cases there was only one ulcer and in 16 there were two or more As will be seen from Barron s report these ulcers appear somewhat more frequently at the two ends of the colon

Because they rarely produce any definite clinical picture their presence is seldom recognized before operation or necropsy Occasionally the ulcer can be seen through the sigmoidoscope In 4 of Barron s the existence of the lesion was not suspected until it perforated

When the ulcer penetrates far enough into the wall of the colon so that the peritoneum is involved there is pain and occasionally this is so severe that a diagnosis is made of acute appendicitis In other cases there is some diarrhea and occasionally with lesions in the left half of the colon there may be hemorrhage

The ulcers that can be seen through the sigmoidoscope can be treated medically those that are situated farther orad must be operated on if they prove troublesome Obviously when they perforate it is essential that the surgeon operate as soon as possible In 37 of the cases reported by Barron the patient died

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nal ileum In the commonest type of this disease the patient develops symptoms of intestinal obstruction with severe abdominal cramps, visible peristalsis and borborygmus He may have complained previously of diarrhea, or of symptoms suggesting appendicitis In other cases the clinical picture is that of chronic ulcerative colitis with anemia and slight fever Not infrequently fecal fistulas appear, or a mass will be felt in the right iliac region At operation the surgeon finds a marked thickening of the last foot or so of the ileum with ulceration of the mucous membrane narrowing of the lumen and perhaps fistulas Some of these fistulous tracts will run from the ileum to the cecum or even to the sigmoid flexure

The disease does not appear ever to be secondary to appendicitis Sections from the inflammatory tissue may show giant cells but they are not typical of tuberculosis, and the injection of material into guinea pigs does not lead to the formation of tubercles

IV A form of localized hypertrophic colitis with or without mild generalized colitis This disease may appear in any part of the colon The wall of the bowel is thickened, and the lumen may be narrowed, the mucous membrane in the affected segment is ulcerated and may show a polypoid change There often are adhesions between the mass and the omentum and surrounding loops of bowel The symptoms are abdominal pain, diarrhea and bloody stools Sometimes there are signs of colonic obstruction

V Inflammatory tissue surrounding solitary penetrating ulcers of the colon or of the last loop of ileum The patient sometimes is operated on under the mistaken diagnosis of acute appendicitis or carcinoma of the colon It is possible that some of these lesions are due to arterial thrombosis

IV Masses due to inflammation in the appendices of the bowel or in diverticula

Chronic typhlitis and perityphlitis are seen occasionally with or without antecedent appendicitis In rare cases the lesions of Hodgkin s disease will be limited to a large extent to the cecum and terminal ileum

Whenever a fecal fistula forms in the region of the cecum the physician must think of actinomycosis and must look for the typical sulphur bodies in the pus

The treatment in the case of most of these lesions is surgical, and the exact procedure must be chosen by the surgeon when the abdomen is open

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Carcinoid Tumors of the Appendix and Small Intestine

The term carcinoid seems to have originated with Obendorfer (quoted by Cooke) who in 1907 presented his observations on seven cases The first case was published by Langhans in 1867 The term is misleading in that it indicates a benign lesion when as will be seen later, metastasis does sometimes take place Even yet there is no agreement as to the origin of these tumors Many authorities hold that they represent a slowly growing carcinoma similar to the basal cell epithelioma of the skin while others feel sure that they arise from the argentaffin cells of the intestinal mucosa

Carcinoid tumors are usually found in persons under thirty five years of age MacCarty has encountered them in one out of every 57 appendices with an obliterated lumen Meyer reported an incidence of 0 42 per cent in 707 cases which is comparable with 0 5 per cent in 8 039 consecutive appendices examined by MacCarty and Magath The tumor occurs in the tip of the appendix as a firm, smooth bulbous enlargement which may be either microscopic or else large enough to be seen readily on gross examination The usual size is from 0 5 to 1 cm

In the small intestine the tumor may be single or multiple Most of them are found in the distal third of the ileum, and only an occasional one is ever seen in the jejunum and duodenum Most of the tumors in the small bowel are nodular but some spread along the transverse axis of the bowel to form an annular mass The cut surface is light yellow On microscopical examination the cells are pale with round nuclei which are fairly uniform in size They are rather rich in chromatin and show a few mitotic figures Although most of these tumors are benign Montgomery and Johnson found reports of at least 9 with metastases and Cooke found that 20 per cent of all the reported small intestinal carcinoid tumors had given rise to metastases Several such lesions have been seen at the Mayo Clinic

In Cooke s series of twenty one malignant intestinal carcinoid tumors obstruction occurred in ten In one the main complaint was cachexia and in another severe anemia In 83 cases of a benign type of tumor clinical evidence of a lesion was present in only 6 Two patients showed symptoms suggestive of appendicitis and 4 had symptoms of intestinal obstruction Only rarely do carcinoid tumors of the appendix produce symptoms or signs and very rarely

Mesenteric Thrombosis and Embolism

Mesenteric vascular occlusion is fortunately a very rare disease At the Massachusetts General Hospital there were thirteen cases in approximately 48 000 surgical admissions The accident may occur at any age, but it is seen most commonly in older people In most cases there is some disease in the circulatory system such as endocarditis, arteriosclerosis, aneurism, phlebitis, or infection in the abdomen It has been seen in several cases of polycythemia

At times practically the whole bowel becomes black and gangrenous In rare cases sufficient circulation is restored so that the patient recovers The most prominent symptom is pain which usually is severe from the outset It is usually at first around the navel, but it soon becomes generalized Sometimes it will stop for a while to return again Vomiting has been observed in about half the cases Occasionally there is diarrhea or tenesmus, and sometimes the stools contain blood Later there is likely to be considerable tenderness and distention but not much rigidity There may be a slight increase in temperature Usually the pulse rate becomes rapid The leukocyte count usually is high soon after the onset of the pain Often the pain is agonizing and symptoms of collapse follow In Meyer s series of 92 collected cases there was a mortality of 57 6 per cent In 9 instances spontaneous recovery occurred In 3 cases the occlusion did not seem to cause any abdominal symptoms, and the condition was found only at autopsy In 43 cases the bowel had to be resected and this was associated with a mortality of 32 6 per cent

The diagnosis is often difficult and all the physician can be sure of is that something very serious has happened in the abdomen, something that has to be attended to surgically and immediately if the life of the patient is to be saved In attempting to make the diagnosis the physician will think of perforation of an ulcer acute pancreatitis volvulus of the bowel an intussusception or some other form of intestinal obstruction Mesenteric embolism or thrombosis will be thought of particularly if the patient is suffering with valvular heart disease or sepsis, or if there are signs of embolism elsewhere, or if the patient is old and markedly arteriosclerotic

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The next objection is that the regurgitation that is observed with a barium enema (which it must be remembered consists of a large amount of fluid that is forced in at the wrong end of the digestive tract and serves to distend the bowel to an abnormal extent) may never take place when small amounts of semi solid material come down normally from above Donaldson who made repeated roentgenologic studies of several persons who voluntarily avoided defecation for four days and who during this time took barium with their food saw no sign of regurgitation into the ileum The sphincter is also wonderfully competent in cases of megacolon

Yet another objection is that the best evidence today indicates that the opening between the ileum and the cecum functions as a sphincter and not as a mechanical valve Those observers who have watched it through a cecal fistula picture it as a mushroom shaped button and not as a pair of lips (Rutherford) Another objection is that for years surgeons have been making ileo-colostomies they have made no effort to build a valve like opening and yet they have heard no complaint about symptoms which could be ascribed to the reflux of colonic contents into the ileum

Finally there is the pragmatic objection that the operative reconstruction of the 'valve has not worked well Case who was associated with Kellogg in his work finally came to the conclusion that when ileo-cecal regurgitation is present in an exaggerated form there is some disease in the colon to account for it and he did not feel satisfied with the results of the operation

The great difficulty that is always encountered in operating on patients who are nervous and run down and who complain of many aches and pains is the impossibility of telling how much is due to the nervousness and constitutional inadequacy and how much to the physical peculiarity that has been discovered Persons of this type will often consider themselves cured for six months or so following any type of operation but after that they generally come back with either the old complaints or else a new set

In 1923 Jones reported sanely and conservatively a study of 1 000 cases in which it seemed possible that the symptoms might be due to a defect in the ileo-cecal sphincter and concluded that operative measures alone were not sufficient to restore the patients to health

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Incompetency of the Ileo cecal Sphincter

As soon as roentgenologists began to give barium enemas to patients, they noticed that in some cases the opaque material ran back into the ileum It next occurred to a few men and particularly to Kellogg, that this regurgitation might be a cause of disease The mucous membrane of the colon absorbs so little that the animal organism is well protected against colonic auto intoxication, but if toxic cecal contents should happen to return to the ileum, where absorption is possible, distressing symptoms might arise Furthermore, it seemed to Kellogg that Nature had designed a valve like structure at the ileo cecal junction and that if in certain patients, he could repair the flaps and bring them into better apposition regurgitation would cease and health would return

Although there may still be something to this attractive theory, there are a great many facts and observations which militate against it In the first place it is now known that regurgitation of a barium enema will take place in perhaps nine out of ten persons, and it would probably take place in all of them if only the material were retained long enough Obviously a phenomenon which can be observed in all persons tested cannot be looked on as a cause of disease unless perhaps in some it is found to be much exaggerated

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The only treatment for all these diseases is surgical removal of the diverticulum

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Tumors of the Peritoneum Retroperitoneal Space Omentum and Mesentery

The tumors of the peritoneum itself are almost invariably secondary to other lesions and the result of direct extension or dissemination Implants may be derived from (1) a papillary cystadenoma of the ovary (2) carcinoma of the stomach (malignant cells may drop down into the peritoneal cavity and give rise to growths which can be palpated through the rectum on the rectal shelf) and (3) a ruptured pseudo-mucinous cyst of the ovary or a mucous cyst of the appendix From these mucous cysts there is produced what is called pseudomyxoma of the peritoneum a condition which is malignant in about 75 per cent of the cases

Rarely there arise in the mesentery solid tumors such as lipomas sarcomas carcinomas and fibromas or cystic tumors of lymphatic gaseous dermoid echinococcic or chylous nature Rawls in 1924 collected records of 100 solid tumors and 200 cysts

Retroperitoneal tumors usually grow from the connective tissue in the posterior abdominal wall The lipomas arising in this region sometimes become very large and their steady growth strongly suggests the presence of a malignant tumor They are usually discovered during middle life and may have their origin in either flank about the level of the kidney The possibility or impossibility of their surgical removal depends largely on their position in relation to neighboring structures

Sarcomas arise from the fascias of the abdominal wall and appear usually during middle life The onset is insidious and at first there may be few symptoms besides fever and vague abdominal distress Later there will be probably some pain and a steady decline in health and strength and weight All these symptoms may appear before an abdominal tumor is palpable

The only solid tumor of the omentum is a sarcoma In all the cases reported so far the patient has died in spite of operation The cystic tumors are lymphangiomas and dermoid and echinococcus cysts

Diseases of Meckel's Diverticulum

Meckel's diverticulum is a relic of the vitelline duct which, in from 2 to 3 per cent of persons fails to become entirely obliterated in embryonic life It is found almost always in the lower part of the ileum from 30 to 90 cm from the ileocecal sphincter, but occasionally it is found farther orad It looks usually like a piece of normal small bowel extending from 2 5 to 10 cm out at right angles from the anti mesenteric border of the gut The vessels which accompanied the vitelline duct may, in rare cases, fail to disappear, leaving cord like remnants which sometimes hang free from the diverticulum They may be attached to loops of bowel, or persist in their normal path to the navel These cords serve occasionally as a cause of intestinal obstruction The diverticulum is usually found opposite the attachment of the mesentery, but it may occur at any point in the circumference of the bowel

This relic of embryonic life will occasionally be the seat of disease It may become invaginated and thus serve as the head of an intussusceptum, or an ulcer may form in it and later bleed or perforate Such complications are more likely to take place in children than in adults Occasionally the ulcers are responsible for massive gastro intestinal hemorrhages These are due to the presence in the diverticulum of a small patch of gastric mucosa which secretes active juice

When hemorrhage takes place, the blood is not as dark or tarry as it is with bleeding from the upper intestinal tract, nor is it as red and clotted as it is with bleeding from the colon

The symptoms of ulceration is Meckel's diverticulum are not pathognomonic. Pain is the most common symptom and usually is referred to the umbilical region Vague, indefinite abdominal distress associated with flatulence may be the main complaint

The *diagnosis* is not easy to make prior to surgical exploration In the case of a recent massive hemorrhage roentgenologic studies will aid in excluding lesions of the stomach duodenum and colon, but it is practically impossible to visualize the diverticulum In the case of a recent massive hemorrhage, roentgenologic examination should be delayed at least a week The physician would want to exclude as possible causes for such bleeding peptic ulcer portal cirrhosis splenic anemia and blood dyscrasias Because in the majority of cases ulceration of Meckel's diverticulum occurs in infancy or childhood, an atypical appendicitis with hemorrhage must also be thought of

Malignant tumors of Meckel's diverticulum are rare, but at least eight cases of sarcoma have been reported The symptoms were those of weight loss, abdominal mass perforation or obstruction and hemorrhage Faust and Walters reported a case in which the only symptom was recurrent hemorrhage with resulting secondary anemia.

Regional Stenosing Enteritis (Terminal Ileitis)

In 1932 Crohn Ginzburg and Oppenheimer[1] brought strongly to the attention of the medical world a disease which they called terminal ileitis and since then many cases have been reported In the last 150 years the disease has been described occasionally under such names as infectious granuloma or inflammatory tumor[2] An excellent review of the subject with a bibliography of 289 titles was prepared in 1939 by Robert Shapiro[4]

Definition — The name terminal ileitis is not entirely suitable be cau e the characteristic lesions are found occasionally in other parts of the ileum and even in the jejunum and colon The four most characteristic features of the disease are (1) the frequent involvement of the last seg ment of ileum (2) the thickening of the wall of the gut with resultant narrowing of the lumen (3) the tendency of the disease to involve short segments of the gut and (4) the granulomatous nature of the lesion

The disease usually is chronic and long lasting The wall of an affected segment of gut becomes so thick that but little lumen is left Common clinical features are attacks of diarrhea occasional fever crampy pains fecal fistulas a mass in the cecal region and perhaps signs of intestinal obstruction

Etiology — The cause is unknown The fact that the disease recurs if at operation bits of diseased tissue are left suggests that the cause is a bacterium or virus No one organism has been found in the lesion uniformly enough to warrant its being looked on as the cause The lesion sometimes resembles that of tuberculosis but tubercle bacilli have never been demonstrated Occasionally a foreign body such as a fish bone or a bit of toothpick is found in the wall of the bowel but usually no such intrusion is present

Before the disease is diagnosed correctly the appendix often has been sacrificed The fact that Crohn[5] has on several occasions seen more than one member of a family with the disease suggests a hereditary or infectious cause

Sex and Age Incidence — In Crohn s series of 110 cases there were approximately three males to two females The average age of the patients when first seen was twenty seven years the age at onset of symptoms was usually from five to fifteen years less than this

Pathology — The disease tends to begin at the ileocecal sphincter and to extend orad usually for from 8 to 12 inches but ometimes for from 24 to 50 inches or more Occasionally there will be diseased segments in the upper ileum and jejunum with apparently normal segments in be tween In the 413 cases collected from the literature by Shapiro the le

The symptoms of all these tumors are often vague and puzzling, many times the only positive finding is that of a mass which can be shown to be outside the gastro intestinal and urinary tracts Roentgenograms may reveal the presence of those bits of bone and teeth which are so characteristic of dermoid cysts

The only possible treatment for all these tumors is surgical The results will depend upon the benignness or malignancy of the tumor and upon the possibility or the impossibility of its removal Although the retroperitoneal lipomas rarely become malignant, the great difficulties which often are encountered in the removal of such large masses, and the tendency which they show toward regeneration if a small fragment is left, cause them to be much feared by the surgeon

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DISEASES OF THE RECTUM AND ANUS

The gastro-enterologist must never forget that an examination of the digestive tract is not complete until the rectum and the anus have been examined with finger and sigmoidoscope and anoscope There is no question that in some cases troublesome constipation and distress of various kinds in the lower abdomen and pelvis can be relieved by the clearing up of extensive cryptitis, the healing of anal fissures the removal of hemorrhoids the excision of fistulous tracts and the dilation of a contracted anal ring For this reason the gastro enterologist should often call in the proctologist to help him with his therapeutic as well as his diagnostic problems It is unfortunate nowadays that many patients with anal or rectal lesions and with all their distress in the pelvis have to pay for many sets of useless roentgen ray films of stomach gallbladder and colon before they can find a clinician who will look carefully at anus and rectum

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in the lumen while others speak of a string sign It is almost pathognomonic

Differential Diagnosis — Given a young person with a history of recurrent episodes of diarrhea fever and abdominal pain with a mass in the right lower quadrant perhaps a fecal fistula and with roentgenological signs of narrowing of the terminal segment of ileum the diagnosis should be easy There may be confusion in cases of non tropical sprue but the roentgenological picture and the appearance of the stools are different in the two diseases Furthermore the anemia of hyperplastic enteritis is seldom severe and rarely of the hyperchromic type

One might think of Hodgkin s disease with large nodes surrounding the ileum but this is a very rare lesion and usually the long history rules it out Tuberculosis of the bowel is not a good diagnosis if there is no sign of the disease elsewhere in the body Crohn believes that the presence of diarrhea helps to differentiate terminal ileitis from acute appendicitis It may be hard to differentiate terminal ileitis from the variety of chronic ulcerative colitis which begins in the cecum

Prognosis — In eight of eleven cases of acute stenosing enteritis seen by Crohn the patient did badly and eventually had to be operated on In the other three cases the patient recovered without operation Patients with the chronic form of the disease tend to drift on for years with recurrent diarrhea and the formation of fistulas Nutrition eventually fails and the patient dies perhaps of peritonitis

Treatment — The treatment depends on the stage in which the disease is encountered and on the condition of the patient In the early acute stages the physician should treat symptomatically and wait to see if the patient will recover and stay well Occasionally one will improve with a smooth diet rest iron and extra vitamins but even then roentgenograms may show that the lumen has become no wider than it was before in fact it may even have become narrower Then because as Crohn says there is no specific medical treatment the diseased bowel should be removed promptly and completely Some surgeons rely on short circuiting the diseased segment or segments but this seems unwise because in ten of twenty cases seen by Crohn this operation did not cure and resection had to be performed later According to Shapiro short circuiting can be expected to cure one out of three patients Resection of all diseased tissue will cure at least two out of three Surgeons have suggested that at least a foot of apparently normal bowel should be removed on either side of the thickened region No attempt should be made to save the ileocecal sphincter as this is likely to lead to recurrence of trouble

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sion was in the terminal ileum in 261 In 100 cases it involved the cecum and ascending colon and in sixteen it was in the jejunum

As H L Robertson points out the most characteristic feature of this type of enteritis is the thickening of the wall of the bowel which leads to a narrowing of the lumen Histologically the lesion is granulomatous in nature Against the theory of a tuberculous origin is the inability of experimenters to infect guinea pigs with bits of diseased tissue Furthermore ileal tuberculosis is seen rarely in persons who have not advanced tuberculosis elsewhere in the body and patients with regional enteritis are not tuberculous

Opposite the diseased segments are large mesenteric lymph nodes which rarely break down or become calcified They so resemble the nodes of mesenteric lymphadenitis that one wonders if there is a common cause for the two diseases Against this idea is the fact that so far no transitions have been seen

When the proximal part of the colon is involved, the question may arise may not the terminal ileitis be due to the same cause that produces chronic ulcerative colitis ? Actually the lesions of chronic ulcerative colitis do not resemble those of stenosing enteritis at all

Symptomatology and Clinical Course — Acute forms of the disease occur with symptoms suggesting some acute intra abdominal inflammation such as appendicitis There will be diarrhea fever a moderate leukocytosis and perhaps an abdominal mass At operation the surgeon finds an edematous reddened and much thickened segment of small bowel The mesentery also will be edematous and thickened and full of large lymph nodes The appendix may be normal or it may be involved in the inflammatory process If the surgeon leaves in a drain he is likely to facilitate the production of an intractable fecal fistula

In the chronic cases the patients have attacks of mild diarrhea with perhaps mucus and occult blood in the stools There may be colicky pain perhaps anemia and occasionally fever Eventually there will be signs of stenosis of the bowel with obstruction cramps borborygmus and visible peristalsis A mass probably will be felt in the right lower quadrant of the abdomen

A common early manifestation of the disease is the appearance of a fecal fistula This may come through the scar left by an appendectomy or it may appear around the anus In other cases the fistulas run from one segment of bowel to another

Roentgenological Findings — The disease can be recognized easily by the roentgenologist because of the narrowed lumen of the terminal segment of ileum Weber[6] speaks of a twisted cord appearance of the barium

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CHAPTER V

DISEASES OF THE LIVER

JAUNDICE

By SIR HUMPHRY ROLLESTON

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lem thus arises whether or not toxic destruction of the reticulo-endothelial cells as in a case recorded by Willmore and Douglas[10] may lead to a complete or partial cessation of formation of bile pigment and so explain some rare cases of acute necrosis and intra hepatic calculi without jaundice

But to resume Mann and his associates[11] (1921–6) in a long series of experiments with a wonderfully successful technique involving less shock and enabling life to be prolonged for 24 hours after extirpation of the liver confirmed Whipple and Hooper s results and proved that in dogs at least bilirubin can be formed by the reticulo endothelial cells outside the liver namely in the bone marrow and spleen These observations establish the reality of a pure extra hepatic jaundice such as hemolytic jaundice in addition to the well recognized obstructive jaundice Between these two forms there is the large category of jaundice in various infective and toxic conditions in which there are various degrees and importance of three factors viz disordered function of the polygonal cells of the liver inflammation and obstruction of the small bile ducts and canaliculi and hemolysis

Here it may be convenient to refer briefly to the estimation of bile pigment in the blood as bearing on the differentiation of the forms of non obstructive jaundice From the use of Ehrlich s diazo reagent Hijmans van den Bergh (1913 1918)[1] came to the conclusion that there are two forms of bilirubin (a) that found in normal bile and in excess in the blood serum and urine in gross obstructive jaundice this form of bilirubin gives with the diazo reagent an immediate direct reaction (b) the bilirubin normally present in small quantities in the blood serum in the local deposits of hematoidin and in hemolytic jaundice this form of bilirubin does not give an immediate direct but an indirect reaction

The polygonal cells of the liver have been thought not to manufacture bilirubin as was formerly believed but to modify and then excrete the bilirubin formed by the reticulo-endothelial cells of the bone marrow spleen and Kupffer s cells in the liver and reaching the polygonal cells of the liver by the blood stream possibly any change in the character of the bilirubin by the polygonal cells is analogous to their influence on fat The difference between the two forms of bilirubin has been ascribed by Hijmans van den Bergh to a physical factor such as adsorption of the form of bilirubin which has not passed through the liver cells to a protein in the blood plasma This was questioned by C H Andrewes[13] (1924) but more recently supported by Barron[14] who found that bile salts and cholesterol which prevent the adsorption of bilirubin by plasma proteins are present in the blood in the forms of jaundice giving a direct van den Bergh reaction Hijmans van den Bergh s test has the advantage over the icterus index test of Blankenhorn (1917)[15] Meulengracht[16] (1921) and Bernheim[17] (1924) in that it is not affected by the presence of carotin and other

The Causation and Classification of Jaundice

Jaundice is the condition recognized clinically by staining of the plasma skin and mucous membranes by bile pigment Like albuminuria it is a symptom of varying significance and may be produced in very different ways

The problem of jaundice has given rise to various classifications which have in common the one division of icterus due to gross obstruction of the bile ducts In obstruction of the large bile ducts the bile, being unable to escape into the intestine, is dammed up in the liver and enters the general circulation either directly through the blood capillaries, after rupture of the bile capillaries, or indirectly through the lymphatics numerous experiments made to settle the route are contradictory, Saunders, Fleischl, Harley, and Szubinski found that ligature of the thoracic duct prevented jaundice, whereas Mendel and Underhill[1] Wertheimer and Lapage, and Whipple and King[3] came to the opposite decision Oertel[4] and Barron and Bumstead[5] conclude that the bile passes by both routes Except for this point the mechanism of obstructive jaundice is clear

Rich (1930)[6] prefers the title regurgitation jaundice instead of "obstructive jaundice as more descriptive of its causation by reflux from the biliary canaliculi of the whole bile into the circulation either because of obstruction to the outflow through the ducts or from necrosis of the liver cells associated with rupture of the canaliculi He gives as the characteristic clinical features of this obstructive or regurgitation jaundice — (1) the presence in the blood plasma of the form of bilirubin which has passed through the liver and gives a prompt direct reaction with Hijmans van den Bergh test (2) subnormal fecal urobilin, and (3) the presence of bilirubin and bile acids in the urine

The question whether or not bile pigment can be formed outside the liver has been much discussed Minkowski and Naunyn s[7] experiments in 1896 on fowls and geese pointed to the liver as the sole site of the manufacture of bilirubin In 1913 Whipple and Hooper[8] after excluding the liver from the circulation, found that hemoglobin injected into the circulation of dogs was promptly transformed into bilirubin At the same time McNee[9] (1913-14) brought forward evidence to show that the cells of the reticulo-endothelial system of Aschoff change hemoglobin into bile pigment The interesting prob-

duction of Rich s retention icterus the combination of excessive formation of bile pigment and diminished excretory power of the liver is essential, for example in pernicious anemia hemolysis provides excess of bilirubin and atrophy of the polygonal cells in the central zone of the hepatic lobule due to anoxemia causes hepatic insufficiency The clinical features of the retention jaundice are (1) the presence of an indirect van den Bergh reaction in the blood serum, (2) increased fecal urobilin and (3) urobilinuria

Jaundice was divided by McNee[19] as has already been stated, into (1) obstructive hepatic jaundice (2) infective and toxic hepatic jaundice (3) hemolytic jaundice Some remarks will be made on each of these three groups and on some special forms of jaundice

1 Obstructive Hepatic Jaundice

Causes of Obstructive Jaundice

The causes of obstructive jaundice may be tabulated under four main headings

1 Obstruction inside the lumen of the ducts gallstones inspissated bile or mucus due to cholangitis either in the extrahepatic ducts or in the small intrahepatic ducts as in some forms of toxic jaundice and in Hanot s biliary cirrhosis Parasites round worms and flukes may enter the common bile duct from the duodenum and hydatid cysts in the liver may rupture into the ducts Most exceptionally carcinoma either of the liver or of the wall of the ducts or gall bladder may extend along the lumen of the duct as a solid cord

2 Changes in the walls of the ducts inflammatory swelling of the mucous membrane in the various forms of cholangitis stricture of the ducts either congenital or acquired primary tumors of the bile ducts papillomas or carcinomas

Spasm of the muscular walls of the ducts has been invoked to explain emotional jaundice and icterus in plumbism Meltzer s[1] disturbance of the law of contrary innervation as a factor in biliary stasis much as it has been disputed explains jaundice due to spasm of Oddi s sphincter at the lower end of the common bile duct This sphincter and the muscular fibres of the gall bladder are antagonistic, and when the gall bladder contracts the sphincter relaxes if from mental excitement or some reflex factor the sphincteric contraction persists during contraction of the gall bladder the pressure of bile in the ducts rises and jaundice which may be prolonged (Nanu Muscel and Pavel[2] Hortolomei and Pavel) and even biliary colic may result

3 Pressure on the ducts from without by tumors enlarged glands and inflammatory adhesions (a) Intrahepatic carcinoma gumma or hydatid may

pigments in the blood serum It distinguishes between frank obstructive and frank hemolytic jaundice, it is extremely delicate and so detects the normal presence of bilirubin in the blood serum, and has a quantitative value in latent jaundice But the value of the test and the biphasic reaction in infective and toxic hepatic ('retention") jaundice has not been so universally useful for these are the cases in which a diagnosis between obstructive and non obstructive jaundice is most often required in order to decide if surgical treatment is indicated Criticism has been directed to the deductions drawn from the direct indirect and biphasic reactions, especially in America, it has been urged that the difference between the direct and the indirect reaction depends merely on the amount of bilirubin present, and the biphasic reaction has been interpreted as evidence of nothing more than the stage of bilirubinemia intermediate between a high and a low icterus index (Snider and Reinhold[18]) A preference has therefore been expressed for the employment of the simpler and more easily applied icterus index

Classifications of jaundice apart from that due to obvious obstruction, have not been entirely satisfactory mixed forms, transitional to obstructive icterus, occur, overlapping of any rigid arrangement has been inevitable, and the classifications and nomenclature have necessarily been influenced by the varying state of current opinion on the question whether or not bile pigment can be manufactured outside the liver In the past there have been descriptions of anhepatogenous hemohepatogenous hemolytic, polycholic, acholuric, pigmentary, infective toxic and other named forms of jaundice In 1922–3 McNee[19] divided jaundice other than that due to obvious obstruction, into two groups — (1) hemolytic, in which as the result of excesssive destruction of red blood corpuscles the reticulo-endothelial cells manufacture more bilirubin than the liver can deal with, and as a result, the amount of bilirubin in the blood increases and jaundice follows (2) toxic and infective hepatic jaundice, in which the polygonal cells of the liver are damaged and so unable to deal with the bilirubin in the blood plasma which would therefore give a delayed direct or an indirect van den Bergh reaction But in many instances there is in addition to the cellular damage obstruction in the bile canaliculi, in these cases the van den Bergh reaction is biphasic, namely gives a slight prompt reaction followed after a variable delav by a gradual depending of the color reaction This has been explained by assuming that some bilirubin fails to enter the damaged liver cells and so passes into the blood while the remaining bilirubin which is excreted by still active liver cells, is obstructed in the bile capillaries and re absorbed into the blood

Rich[20] (1930) included in one group all jaundice not due to obvious obstruction, and called this retention jaundice ', an unfortunate term as in the past it has been used to describe obstructive or mechanical jaundice For the pro-

turning them down and compressing them with a glass slide it then spreads to the face neck body and limbs It is easily missed in artificial light, and the pingueculæ or masses of fat in the conjunctivæ must not be hurriedly regarded as evidence of icterus In chronic cases the skin may become dark green and xanthoma or xanthelasma described by Chauffard[25] as tophi of cholesterol may form either in flat patches or nodular areas which may be painful Spiderlike angiomas are also common and hepatic insufficiency causes hemorrhages The urine shows the presence of bile pigment and salts twenty four hours before the conjunctivæ become icteric but the presence of both bile pigments and salts in the blood and urine (complete jaundice) is characteristic of absolute obstructive jaundice although the bile salts may disappear from the urine later on (dissociated jaundice) The color of the urine varies from intense yellow to dark brown or in rare cases almost black and may vary during the day in a remarkable manner In some convalescent cases although the skin is still yellow the urine is free from bile With absolute obstruction urobilinogen is absent from the urine but when some bile enters the intestine there may be urobilinogenuria from bacterial activity in the intestine and from hepatic insufficiency which results in a failure of the transformation of urobilin into bilirubin There may also be indicanuria Casts and mucin (nucleoprotein) are commonly present in the urine in well marked jaundice but albuminuria is rare except in the presence of considerable cholemia

In complete obstruction the feces are bulky acholic and extremely offensive mainly from the presence of fatty acids the amount of undigested fat being increased from the normal ten per cent to fifty five per cent or even seventy eight per cent The clay color of the feces is due partly to fat and partly to wide infiltration with bubbles of gas The other secretions are usually free from bile the saliva is tinged only when there is some inflammatory process in the mouth such as stomatitis the sweat in the armpits is sometimes jaundiced tears and women s milk more often than not are unstained Usually the cerebrospinal fluid is unaffected

It has always been accepted that a slow pulse is characteristic of uncomplicated jaundice and that it may be irregular particularly in catarrhal jaundice This was disputed by Mackenzie[26], and any slowing or irregularity has been regarded as due to rest in bed or as independent of jaundice (Windle[7]) According to John Thomson [8] jaundiced children do not show slowing of the pulse The cause of the bradycardia has been ascribed to the bile acids or to the bile pigments and their action on the myocardium or on the cardiac ganglia or to central stimulation of the inhibitory fibers of the vagus The rate of the pulse may quicken by twenty beats when the patient sits up The blood pressure is low a mitral systolic murmur due to muscular incompetence may be audible and the second sound over the pulmonary area accentuated

compress a bile duct, and there may be jaundice, although bile passes from the unobstructed ducts into the intestine and the feces retain their normal color, but the jaundice is probably due, not to the local biliary stasis, but to some widespread damage to the liver cells or to hemolysis (McMaster and Rous[3])

(b) Enlarged glands in the portal fissure, secondary to carcinoma of the liver, gall bladder, or stomach, or due to tuberculosis, syphilis, or lymph adenoma may compress the hepatic ducts and produce jaundice without dilatation of the gall bladder Similar enlargement of the glands near the head of the pancreas will cause jaundice with distention of the gall bladder as in malignant disease of the head of the pancreas Gummatous change in the portal fissure or around the head of the pancreas has corresponding effects These are rare causes, in 1925 Jean[4] collected six cases of chronic jaundice due to tuberculous glands

(c) Perigastric or periduodenal adhesions and cicatrization in rather rare instances involve the ducts and cause chronic jaundice More often carcinoma of the pyloric end of the stomach spreads up the lesser omentum and compresses the common bile duct

(d) Pancreatic lesions carcinoma of the head of the pancreas causes a characteristic train of symptoms namely progressively deepening jaundice with a very gradual painless onset distention of the gall bladder, rapid emaciation, and death within six months of the onset Chronic pancreatitis, usually due to a stone in the common duct may, after the stone has been passed persist and in the 62 per cent of cases in which the common bile duct runs through, instead of behind the head of the pancreas give rise to jaundice Acute catarrhal pancreatitis such as probably occurs in ascending infection from the duodenum and in mumps may cause jaundice, as also may a hydatid cyst in the head of the pancreas a large calculus in Wirsung s duct, and occasionally a pancreatic or peripancreatic cyst

(e) Retroperitoneal tumors and those arising from the right kidney or adrenals may compress the common bile duct

(f) Aneurysms of the hepatic artery the aorta and even the superior mesenteric artery may also compress the common bile duct

4 Kinking or torsion of the ducts may be due to various causes, especially a floating right kidney hepatoptosis gastroptosis and a wandering spleen Possibly abdominal tumors, such as ovarian cysts and uterine fibromyomas, constipation, and intestinal flatulence may occasionally act in this way

Clinical Picture of Obstructive Jaundice

Jaundice is usually first visible in the conjunctivæ, and can be seen about the same time in the mucous membrane of the hard palate or in the lips by

function of the liver and from acidosis Hemorrhages occur into the skin from mucous membranes and in very rare instances into the brain This hemorrhagic tendency renders operative interference a very anxious proceeding

The diagnosis prognosis, and treatment of the various forms of obstructive jaundice are described *elsewhere under the headings of the conditions responsible*

Infective and Toxic Hepatic Jaundice

A few remarks may be made on the general characters of infective and toxic hepatic jaundice especially as contrasted with obstructive jaundice The jaundice is a symptom of some underlying infection or intoxication such as *septicemia pneumonia chloroform phosphorus* or arseniuretted hydrogen poisoning The jaundice is subordinate to the constitutional symptoms and is often slight The amount of bilirubin in the blood and urine is less than in obstructive jaundice bile salts are often absent (dissociated icterus) the blood serum gives a biphasic or varying reaction for bilirubin with van den Bergh s test and urobilinuria which has been regarded as evidence of hepatic inadequacy is usually present Albuminuria fever splenic enlargement and evidence of grave toxemia such as hemorrhages drowsiness delirium and the typhoid state may appear The clay colored stools slow pulse and pruritus of obstructive jaundice are absent, and the disease runs a shorter and more violent course

There are many forms of acute infective jaundice especially during war time when it is commonly epidemic This jaundice of campaigns may be due to infection with B coli B typhosus or paratyphosus and very probably to other microorganisms The syndrome formerly known as Weil s disease and once regarded as due to B proteus fluorescens is now generally thought to be in the main spirochetosis icterohemorrhagica, though other forms of infective jaundice have probably been included under the heading of Weil s jaundice

Common Infective Hepatic Jaundice

Synonym Catarrhal Jaundice

Definition — A form of infective jaundice usually benign due to an unknown infection of the liver and the bile ducts and occurring sporadically as well as in epidemic

The common catarrhal jaundice was formerly considered to be due to obstruction at the lower end of the common bile duct caused by inflammatory swelling of the mucosa extending from the duodenum with a plug of mucus in

The blood plasma contains bilirubin and bile salts Van den Bergh's test gives an immediate direct reaction for bilirubin in the blood serum, which may reach the high figure of 1 in 4,000 (50 units) The degree of jaundice is no guide to the bilirubin content of the blood at the time When the bile salts without bile pigment pass into the intestine (dissociated jaundice) the blood shows the normal hemoconia, or minute particles of fat, an hour and a half after a meal, whereas in complete obstruction hemoconia cannot be seen with the ultramicroscope (Brule[29]) There is not necessarily anemia or leukocytosis, though the latter may be present in cholemia and of course in the presence of infection In grave cholemia the red cells may show granular degeneration The red cells are larger than normal and show an increased resistance to hypotonic salt solutions (Chauffard), thus contrasting with chronic hemolytic jaundice The cholesterol content is increased, and in severe cases the alkalinity diminished Respiration is often slowed, and apart from complications the temperature is not raised The liver is often increased in size from retention of bile but the spleen is usually normal The condition of the gall bladder is an important element in diagnosis, it is distended in obstruction of the common duct by malignant disease, collapsed or at any rate not palpable in gallstone obstruction (Courvoisier's law)

Symptoms apart from the underlying causes of jaundice, are due to the hepatic insufficiency and in some degree to the presense of bile in the circulation The bile salts have been thought to account for mental depression, pruritus, and slow pulse but otherwise they cannot be considered as an important factor in the production of symptoms Xanthopsia which might be reasonably explained by absorption of the blue and violet rays by media containing bilirubin, does not show any relation to the degree of jaundice it may be absent in deep jaundice and present in cases with slight icterus, and it can therefore be better connected with toxic disturbance of the retina Pruritus is said to occur in from twenty (Frerichs) to fifty (Cabot[30]) per cent of the cases Its cause is not known it may be preicteric and disappear with the onset of jaundice or be continued indefinitely, and in the same patient one attack of jaundice due to gallstones may be accompanied by itching while another is not Bile salts, pancreatic disease (Robson[31]) the dry condition of the skin and malignant disease have been suggested as causes but it seems more probable that it is due to some form of hepatic toxemia as it promptly ceases when a free exit for bile is provided The high cholesterol content of the blood is connected with the occurrence of xanthoma and with the formation of gall stones, but cannot be correlated with the occurrence of grave nervous symptoms which are best explained by hepatic insufficiency and the flooding of the circulation with poisons absorbed from the alimentary canal drowsiness headache, delirium and coma may thus result from failure of the detoxicating

function of the liver and from acidosis Hemorrhages occur into the skin from mucous membranes and in very rare instances into the brain This hemorrhagic tendency renders operative interference a very anxious proceeding

The diagnosis prognosis and treatment of the various forms of obstructive jaundice are described elsewhere under the headings of the conditions responsible

Infective and Toxic Hepatic Jaundice

A few remarks may be made on the general characters of infective and toxic hepatic jaundice especially as contrasted with obstructive jaundice The jaundice is a symptom of some underlying infection or intoxication such as septicemia pneumonia chloroform phosphorus or arseniuretted hydrogen poisoning The jaundice is subordinate to the constitutional symptoms and is often slight The amount of bilirubin in the blood and urine is less than in obstructive jaundice bile salts are often absent (dissociated icterus) the blood serum gives a biphasic or varying reaction for bilirubin with van den Bergh s test and urobilinuria which has been regarded as evidence of hepatic inadequacy is usually present Albuminuria fever splenic enlargement and evidence of grave toxemia such as hemorrhages drowsiness delirium and the typhoid state may appear The clay-colored stools slow pulse and pruritus of obstructive jaundice are absent and the disease runs a shorter and more violent course

There are many forms of acute infective jaundice especially during war time when it is commonly epidemic This jaundice of campaigns may be due to *infection with B coli, B typhosus or paratyphosus and very probably to* other microorganisms The syndrome formerly known as Weil s disease and once regarded as due to B proteus fluorescens is now generally thought to be in the main spirochetosis icterohemorrhagica though other forms of infective jaundice have probably been included under the heading of Weil s jaundice

Common Infective Hepatic Jaundice

Synonym Catarrhal Jaundice

Definition —A form of infective jaundice usually benign due to an unknown infection of the liver and the bile ducts and occurring sporadically as well as in epidemics

The common catarrhal jaundice was formerly considered to be due to obstruction at the lower end of the common bile duct caused by inflammatory swelling of the mucosa extending from the duodenum with a plug of mucus in

the lumen although opportunities for confirming this after death are rare, and its existence has been very seriously questioned (Graham, Cole Copher and Moore[3]) this condition is referred to elsewhere as acute catarrhal choledochitis But as most cases of so called "catarrhal jaundice appear to be due to an infective hepatitis the latter condition will be considered here, especially as these cases may pass into acute necrosis of the liver On the other hand, it is much like jaundice due to local obstruction, and a biphasic van den Bergh reaction[19] shows that obstruction may be present at certain periods of so-called catarrhal jaundice The two conditions are certainly rather confused together and probably overlap, but on the whole there seems to be little doubt about the similarity of the sporadic and epidemic cases of the disease Epidemics occur in war and also sometimes apparently at the time that influenza is prevalent It has been suggested that epidemics are spread by carriers and that the infection is due to fecal contamination (Costa and Troisier[33]) There is not any hard and fast line between the severe cases in this category and acute necrosis (yellow atrophy) of the liver (Cockayne[34])

Bacteriology

Various microorganisms, especially of the colon typhoid group, and particularly atypical paratyphoid microorganisms, have been incriminated but the responsibility of the paratyphoid variant has given rise to considerable difference of opinion A virus, not pathogenic for monkeys and smaller laboratory animals has been suggested for the epidemic form, and the complication of acute necrosis has been explained by a superimposed toxæmia in a patient whose liver has not fully recovered from the virus infection (Findlay, Dunlop and Brown[35])

Morbid Anatomy

The changes are rather conjectural as the fatal cases usually show the lesions of acute necrosis (yellow atrophy) of the liver Short of this there is parenchymatous degeneration of the liver cells

Clinical Picture

There is first fever and malaise which may be regarded as influenza until bile appears in the urine or the conjunctivæ are noticed to be icteric The blood serum will show an increased bile index before jaundice appears in the skin or urine Loss of appetite is the rule, but nausea, vomiting and loose stools are probably more closely associated with acute catarrhal choledochitis

than with the condition now under consideration The liver and the spleen are usually moderately enlarged and the liver may be tender The arterial blood pressure is low and the pulse is slow In the epidemic jaundice of Gallipoli in the Great War dilatation of the right side of the heart was noticed (Hurst[36] Willcox[37])

Itching of the skin which sometimes precedes obvious jaundice may be very troublesome and like the mental depression which is often prominent is probably due to toxins which the liver fails to stop The feces are usually pale and devoid of bile at least for a time From duodenal lavage Jones and Minot[38] find that the early stage in which the duodenal contents show little or no bile is followed by a long phase accompanying clinical improvement of an excessive output of bile due to disordered function of the liver cells as shown by the appearance of an abnormal pigment cholecyanin With his serum modification of the phenoltetrachlorphthalein test Rosenthal[39] found evidence of severe disturbances of hepatic efficiency The urine shows the presence of bile pigment the blood contains bilirubin and van den Bergh s test shows a biphasic reaction pointing to a combination of obstructive and toxi infective jaundice (McNee[19])

There is anemia with a leucopenia especially of the polymorphonuclears so that there is a relative lymphocytosis (Jones and Minot[34] Thewlis and Middleton[40]) According to Jones and Minot the total number of red cells and the hemoglobin show a fall In the early stage there may be a leucocytosis followed by leucopenia with at the height of the jaundice a relative increase of lymphocytes (50 per cent) and of the large mononuclears immature and vacuolated leucocytes are common (Thewlis and Middleton) There is loss of weight from inability to digest food generally and especially fats Relapses apparently due to errors in diet especially a rapid return to solid food when there is gastro-intestinal disturbance or exposure to cold may occur The duration varies greatly in different cases the jaundice may have disappeared in three or four weeks, or it may last for several months

Prognosis

As the condition may pass into acute necrosis (yellow atrophy) of the liver some reserve is advisable but generally speaking the outlook is so good that any outspoken warning is unnecessary

Diagnosis

While the great majority of the cases designated as catarrhal jaundice are probably due to hepatic infection it would in the present state of our knowl

edge be unwise to rule out the occurrence of a catarrhal inflammation of the biliary papilla the lower end of the common bile duct, or the head of the pancreas Such a cause is suggested by those cases preceded by vomiting and diarrhea, though such a sequence of course in no way excludes infective hepatitis The existence of some infective disease, such as influenza, is a help to diagnosis

The early jaundice of syphilis, which is only a special form of the same condition often coincides with the roseola and is very resistant to ordinary treatment In middle and later life jaundice should arouse suspicions of gall stones and of malignant disease, and it may be pointed out that the permanent jaundice of malignant disease may be ushered in by jaundice preceded by acute gastro intestinal disturbance Several relapses, particularly with transient fever should suggest the presence of gallstones with further investigation from this point of view such as an x ray examination Deep or black jaundice points to malignant disease

Treatment

The patient should remain in bed on a simple, but not starvation, diet and should take a fair quantity of sugar and carbohydrate food, in order to improve the nutrition and resistance of the liver cells as Whipple has shown experimentally to take place In the presence of gastric irritability the diet should be fluid but experimental observations do not show that increased diuresis leads as has been thought, to a greater elimination of bilirubin in the urine Vichy water, barley water, whey sweetened lemonade, peptonized or citrated milk should be given at first, followed by milk gruel milk toast minced chicken or fish rice pudding

Fatty food yolk of eggs and other foods rich in cholesterol should be avoided By his method of non surgical drainage and the removal of mucus plugs from the common bile duct Vincent Lyon finds that recovery from simple catarrhal jaundice is accelerated

For gastric irritability warm compresses bismuth and dilute hydrocyanic acid and sodium bicarbonate should be prescibed Constipation should be met by enemas or salines especially magnesium sulphate in concentrated solution, but vigorous purges are unnecessary For flatulence minute doses of calomel (1/20 gr , 0 003 gm) salicylate of bismuth salol mixed with magnesium carbonate, or powdered charcoal may be prescribed For itching of the skin ichthyol thyroid extract calcium lactate internally and local applications of carbolic acid solution (1 in 60) or hypodermic injections of atropin (1/100 gr , 0 0006 gm), or pilocarpin (1/8 gr , 0 008 gm) should be tried Alkalies are preferable to acid tonics

Spirochetosis Icterohemorrhagica

In 1916 it was definitely proved by Inada Ido Kaneko and Ito[41] that a disease in Japan presenting the symptoms of Weil s disease was due to the spirocheta icterohemorrhagiæ This observation has been widely confirmed the existence of the infection being described in Flanders by Stokes and Ryle[42] in the same year Noguchi[43] showed that the Japanese Belgian and American strains of the organism are identical and, as it differs from all other spirochetes both morphologically and in resisting the destructive effect of a ten per cent solution of saponin described it as a separate genus leptospira icterohemorrhagiæ For a description of this condition see Chapt XXX in Vol V

Icterus Gravis

This is a general term for cases of severe jaundice due to various factors inducing acute necrotic degenerative or autolytic changes in the liver cells and characterized by the symptoms of rapid hepatic insufficiency It thus includes acute necrosis (yellow atrophy) subacute atrophy phosphorus poisoning severe spirochetal (icterohemorrhagic) jaundice yellow fever and the acute forms of diffuse hepatitis due to streptococcic staphylococcic and other infections which may attack the liver especially when it is previously damaged

Acute yellow atrophy is a special form characterized by the predominance of the necrosis and contrasts with phosphorus poisoning in which there is an equally characteristic increase in size But as the essential symptoms, namely those of grave hepatic insufficiency are described under the heading of acute necrosis it is unnecessary to give a separate account of them here Jaundice may be the most obvious feature in cases of acute infective hepato-renal insufficiency in which the lesions in the kidney are much more advanced (Merklen[44]) Such cases have been described as acute nephritis with jaundice and are due to both organs suffering concomitantly from toxemia or infection such as spirochetosis icterohemorrhagica or pneumococcemia (Roussel and Lavergne[45]) They thus differ from cases of icterus gravis in which the renal disorder is subordinate to the hepatic

Acute Necrosis (Yellow Atrophy) of the Liver

Definition —An acute autolytic necrosis of the liver cells with progressive diminution in the size of the organ, jaundice nervous disturbance and commonly a fatal termination If death does not occur the liver passes into the condition of subacute atrophy

Etiology

The disease has always been rare, but it has become less so since the introduction of arsphenamin and the occurrence during the war of poisoning by trichlorethane and trinitrotoluene In 1903 Best collected 450 cases

Age — It is commonest between twenty and thirty A certain number occur in the first decade of life, I have collected forty three of these cases Degener and Jaffe[46] recorded extensive necrosis of the liver in a stillborn male infant Subacute atrophy, in which there is considerable compensatory hyperplasia of the liver cells, is more often seen in the young

Sex — Women are more often attacked than men on account of the disposing influence of pregnancy The anxiety, especially in unmarried women, induced by pregnancy has been thought to lower the general resistance and so no doubt increases the virulence of the toxemia of that condition

Acute necrosis is a subdivision of icterus gravis and, like it, is not a specific disease but a symptom complex due to various causes The relation of an antecedent condition appears to be definitely etiological in some cases but in others the cause is uncertain Some inherent or acquired want of resistance on the part of the liver is probably important in enabling various microbic or other poisons to cause acute necrosis The jaundice of the early stage of syphilis in rare instances passes into acute atrophy, in 1921 Herxheimer[47] collected sixty nine cases in which the influence of arsphenamin could be excluded It does not appear to be proved that the Treponema pallidum is present in the liver it may therefore be due to poisons produced elsewhere by the treponema (Fischer[48]) or as S MacDonald[49] suggested to microorganisms derived from the alimentary canal acting on a liver with its power of resistance diminished Rather closely allied are the cases now considerable in number, of changes resembling acute yellow atrophy following the intravenous injection of arsphenamin for syphilis Here again we are met by the possibility that the exciting cause is some superadded infection which is favored by the impaired resistance of the liver In Germany during the years immediately following the Great War, jaundice and acute necrosis even apart from the influence of syphilis and arsphenamin injections became more frequent In Great Britain during the same period, there was not any such increase There may be a considerable latent interval between the completion of arsphenamin treatment and the onset of acute necrosis

Toxic jaundice and acute or subacute necrosis have also followed the use of cinchophen (atrophan) a derivative of quinoline carboxylic acid This substance, employed in 1908 by Dohrn and Nicolaier[50] to increase the output of uric acid, has been largely used for the relief of pain and is a constituent of many popular 'rheumatic cures Toxic jaundice as a result of its use was first recorded in 1923 by Worster Drought[51], subsequently Willcox[52] (1926) and

others reported fatal cases and in 1932 Parsons and Harding[53] collected 32 fatal cases, in 26 of which necropsy showed that the essential morbid changes were confined to the liver. Even quite small doses have produced these lesions presumably as the result of idiosyncrasy or acquired hypersensitiveness (Reichle).[54] The onset of symptoms due to hepatic lesions may, as in arsphenamin poisoning, be delayed. It has been thought that regeneration of the liver cells occurs more slowly than in other forms of hepatic necrosis (Beaver and Robertson).[55] Early in the war trichlorethane used as a dope for aeroplanes and for a longer period trinitrotoluene produced acute necrosis among the workers. Delayed chloroform poisoning in rare instances may be accompanied by the lesions of acute necrosis, but this is so rare that some additional factor such as infection is highly probable; this view is supported by Opie's[56] experimental production of acute atrophy by the combined action of chloroform and bacteria (streptococci, B. coli). In one case Pauly[57] ascribed acute necrosis to poisoning by melinite which contains picric acid.

Alcoholic excess in a few instances has been followed by acute necrosis and here again it may act by reducing the resistance of the organ and so allowing some infection to fall on the liver. Pregnancy is undoubtedly an antecedent condition of importance and is prone to induce changes in the liver and so reduce its resistance; the toxemia of pregnancy may fall chiefly on the liver. Various infections may arise during pregnancy and would then find the liver less resistant. Previous disease of the liver, such as cirrhosis, chronic venous engorgement and the chronic parenchymatous hepatitis of Graves' disease (Weller[58]) occasionally act in the same manner. In rather rare instances acute necrosis has followed acute infections such as typhoid, influenza and septicemia, but possibly in such cases the liver was wanting in vitality.

Microorganisms, usually B. coli, but also streptococci, staphylococci, pneumococci and spirochetes (Hayashi and Kibata[59]) have been found, but not so constantly as to justify any definite conclusion.

Morbid Anatomy

The appearances differ in acute cases from those in the subacute type in which some regeneration of the liver cells has taken place. In the most acute cases the liver is much reduced in size and may weigh one half or one third only of its normal weight. Though usually uniform, the atrophy may be more advanced in the left than in the right lobe. The organ seems to have shrunk within its capsule, which is wrinkled, readily thrown into folds by the impact of a stream of water, can be easily picked up and peels off easily. There may be subserous hemorrhages and externally it is yellowish green splashed with dark red areas. The organ is flabby and collapses so as to lie flat on the post mortem

table It cuts like collapsed lung and the section shows a predominating yellowish color mottled with red areas which are depressed below the surface of the yellow areas, the outlines of the lobules being lost, but in some instances red is the predominating color In cases of subacute atrophy that have survived a considerable time the surface of the organ shows yellow or greenish nodules due to compensatory regeneration The bile ducts usually contain mucus only, but there may be bile in the gall bladder The amount of fat in the liver is not increased either chemically or microscopically, the yellow color being due to bile staining The water and amino acids, due to autolysis of the hepatic cells, are increased

Microscopically the changes may be so extreme that it is difficult to recognize the organ They are more advanced in the red areas, which are older, than in the yellow tracts The liver cells in the intermediate zone of the lobules are the first to become granular, bile stained and show fragmentary degeneration of the nuclei which lose the power of staining before the cytoplasm The cells undergo necrosis become separated by hemorrhage, and the small bile ducts show proliferation and degeneration of their cells In the red areas absorption of the autolysed liver cells has taken place and there is little recognizable liver tissue except the fibrillar vascular framework of the organ enclosing red blood corpuscles and debris There may be varying amounts of small cell infiltration around the portal canals

In cases not proving fatal rapidly the surviving liver cells at the periphery of the lobules show compensatory hyperplasia The cells become larger may contain several nuclei and divide by direct and indirect nuclear division This hyperplasia leads to the formation of nodules or adenomas seen in subacute atrophy as prominent projections on the depressed surface of the organ In addition the pseudobile canaliculi are prominent and have been regarded as a means of compensatory hyperplasia The interstitial tissue multiplies so that a subacute cirrhosis follows This is the condition of subacute atrophy which is more often seen in the young and probably accounts for some cases of cirrhosis in children When the compensatory hyperplasia is well marked, the condition is sometimes called multiple nodular hyperplasia (Miller and Rutherford[60]) All the organs are bile stained The spleen is softened and usually somewhat enlarged The kidneys show degeneration or necrosis of their epithelium The heart is softened Hemorrhages are scattered throughout the body

Pathogeny

The process is an acute necrosis with autolysis of the liver cells This is very probably due to poisons destroying the liver cells but not their autolytic ferments which then act on the dead cells (H G Wells[61])

Clinical Picture

The symptoms are grouped in two stages in the first they are those of jaundice preceded as a rule by some days of malaise This condition which resembles and is naturally often regarded as benign jaundice usually lasts for five or six days but in rare instances persists for weeks this may occur in syphilitic subjects The onset is insidious but there may be some fever

The second stage comes on suddenly with the appearance of grave symptoms pointing to implication of the nervous system and general toxemia Severe headache restlessness twitching delirium screaming convulsions transient paralyses squint dilated pupils and urgent vomiting may well suggest meningitis The plantar response is extensor The jaundice varies in degree and in rare instances is said to be absent this may depend on degeneration of Kupffer s cells The skin may show a red rash or hemorrhages and blood may be found in the vomit feces and urine Epistaxis and menorrhagia may occur At the onset of the grave or typhoid symptoms the liver may be enlarged either from acute changes or from pre existing disease but however this may be the hepatic dullness progressively diminishes the flabby liver drops away from the abdominal wall and flatulent intestines take its place It is difficult to be certain about the size of the organ by ordinary clinical methods By x ray examination Strathy and Gilchrist[6] found that in nine out of ten cases of acute necrosis almost all in patients who had arsphenamin the upper surface of the liver was more dome shaped than normal and that the angle formed by the junction of the liver and the vertebral shadows was acute instead of the normal right angle In about a third of the cases the liver is tender Ascites is rarely detected but may be found in small amounts after death Moderate splenic enlargement is occasionally palpable The temperature varies but is more often low than raised It may rush up before death and I have seen it rise from 93 to 110 F just before death As a result of vomiting the blood may be concentrated and the red blood count increased a slight leukocytosis may be present The coagulation time of the blood is prolonged and bile pigment is present in the plasma The cholesterol content of the blood is diminished as is the blood sugar

The urine is somewhat diminished in amount highly colored from bile pigments and urobilinogen contains albumin bile stained casts and sometimes blood glycosuria does not occur The urea is diminished and the ammonia increased from acidosis and the resulting fixation of the ammonia by organic acids Leucin as rounded discs which must not be confused with starch granules from dusting powder and tyrosin as needle shaped crystals may be but

are not invariably found in the urine In order to demonstrate them it may be necessary to concentrate the urine They are due to autolysis of the liver cells and also to inability of the greatly damaged liver to de aminize amino acids at even an ordinary rate (Stadie and Van Slyke)

The typhoid stage usually lasts a few days, I have seen death occur twenty four hours after the onset of jaundice In rather rare cases jaundice is much prolonged or may pass into convalescence More than half the cases terminate fatally within two weeks death being preceded by coma with stertorous breathing and incontinence

The subacute cases are those in which the second stage is prolonged or in which convalescence appears to follow In some cases jaundice persists but death does not occur for months or even years and then the changes of nodular hyperplasia are found In some of these cases the clinical features are those of rapid cirrhosis with ascites

Diagnosis

The diagnosis depends on jaundice with progressive diminution in the size of the liver and severe constitutional and nervous symptoms Diagnosis usually is easy From other forms of icterus gravis the distinction consists in the diminution in the size of the liver In phosphorus poisoning the liver is much enlarged, the gastric disturbance is more prominent the nervous symptoms less in evidence and jaundice appears after the acute gastric symptoms instead of being an initial manifestation In phosphorus poisoning the history may give valuable information Fatal jaundice due to trinitrotoluene produces acute atrophy, but this form may be recognized by the history and by Webster s test for trinitrotoluene poisoning In severe forms of spirochetal (icterohem orrhagic) jaundice there are constitutional symptoms and fever precedes by some days the appearance of jaundice and the spirochete can be found in the urine

Prognosis

Formerly doubt was thrown on the cases that were not fatal but the recog nition of subacute cases which have been known to survive for considerable periods and then to show typical morbid changes, makes it reasonable to believe that in other instances recovery may occur The subacute cases are seen chiefly in the young, probably from their greater power of repair, and the outlook is therefore less grave in early life It is extremely bad in pregnant women, in cases with rapid disappearance of the liver dullness, and with a very high or very low temperature The condition of the kidneys is most important

failure in the urinary output much albuminuria, hematuria, and numerous casts render the prognosis very gloomy

Treatment

Prophylaxis should be employed in conditions in which acute yellow atrophy may occur Thus as chloroform exerts an autolytic action on the liver jaundice in pregnant women should contraindicate chloroform anesthesia in child birth and the use of chloral and chloretone In arsphenamin treatment it has been urged that routine examination of the blood for latent jaundice by van den Bergh s test or by the method of determining the bile index is of value in providing a danger signal for cessation of the injections and for the free administration of glucose to protect the liver cells (Gerrard[63]) Experimental evidence that calcium salts protect against hepatic necrosis suggests their use (Minot and Cutler[64])

The use of sodium thiosulphate in the early stages of jaundice from arsphenamin has been recommended to prevent the development of acute yellow atrophy It is given intravenously 0 6 gm in 20 c c of distilled water daily for four doses and then every other day until jaundice disappears In catarrhal jaundice with drowsiness measures should be taken to diminish toxemia and obviate the onset of acidosis namely purgation intestinal antiseptics and diuretics on the one hand and chocolate sugar and alkalies on the other

When the disease is definitely established plenty of water with sugar should be given intravenous injection of glucose (8–20 per cent) solution supplemented by insulin may be tried Vomiting should be combated by bismuth small doses of cocain or small hypodermic injections of morphin

Acidosis may also be met by alkalies given by the mouth rectum, subcutaneously or intravenously Constipation should be corrected by enemas and intestinal putrefaction and fermentation treated by a milk diet and antiseptics such as salol calomel gr 1/ 0 (0 003 gm) and naphthalene tetrachloride

Phosphorus Poisoning

Phosphorus may be taken with suicidal intent or more rarely by accident Match heads may be made up into an emulsion or rat paste may be swallowed Accidental poisoning may be due to eating rat paste or animals e pecially poultry, which have fed on vermin killed by phosphorus in rare instances fatalities have followed medicinal doses and the application of phosphorescent paste to the skin

are not invariably, found in the urine In order to demonstrate them it may be necessary to concentrate the urine They are due to autolysis of the liver cells and also to inability of the greatly damaged liver to de aminize amino-acids at even an ordinary rate (Stadie and Van Slyke)

The typhoid stage usually lasts a few days I have seen death occur twenty four hours after the onset of jaundice In rather rare cases jaundice is much prolonged or may pass into convalescence More than half the cases terminate fatally within two weeks, death being preceded by coma with stertorous breathing and incontinence

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coagulation time is prolonged and its fat content increased Usually there is little or no fever The outlook is extremely grave

Diagnosis

The history that phosphorus ha been taken is important but in its absence the occurrence of severe gastric symptoms before the appearance of jaundice i sugge tive The diagnosis from acute necrosis has already been di cussed The condition in its later stages is like that produced by iodoform or delayed chloroform poisoning

Treatment

If the patient is seen soon after the poison has been taken the stomach should be washed out with a solution of permanganate of potassium (0 5 to 2 per cent) or peroxide of hydrogen (1 to 3 per cent) or sulphate of copper to form the comparatively harmless oxides of phosphorus Old French or oxidized oil of turpentine 40 minims (3 c c) in an emulsion should be given four times in the first hour and three times daily afterwards The bowels should be opened but castor oil and all fats which render phosphorus soluble should be avoided The treatment for the grave symptoms of the second stage is the same as in acute necrosis

5 HEMOLYTIC JAUNDICE

Hemolytic jaundice is a dissociated icterus with an increased bilirubin con tent of the blood serum without any corresponding increase of the bile salts and cholesterol or as in the phrase of the French school a pure pigmentary cholemia When from excessive hemolysis bilirubin is formed by the reticulo-endothelial cells in quantities too large for the polygonal cells of the liver to deal with some of the bilirubin passes straight into the hepatic blood vessels and causes jaund ce, while that acted upon by the polygonal cell escape into the intestine and colors the feces

In true hemolytic jaundice the bilirubin content of the blood never equal that in obstructive icterus the blood serum gives a negative or delayed direct reaction with Hijmans v d Bergh s test bile pigment does not appear in the urine so that the condition is often called acholuric jaundice and the jaundice is never deep or black The icterus is an incident of an underlying proce s such as infection intoxication or metabolic error and does not of itself give rise to symptoms

Hemolytic jaundice may be acute in grave hemolysis such as that accom

Morbid Anatomy

All the organs show fatty change, but especially the liver, and there are numerous hemorrhages throughout the body, fat embolism causing areas of necrosis The liver is larger than normal, firm but friable and of a saffron yellow color with some hemorrhages In exceptional instances the organ has been described as showing the changes found in acute yellow atrophy The fat content is much increased from the normal three per cent and may be as high as thirty per cent It is due to the transport of fat from other parts of the body

Microscopically the liver cells are in a state of advanced fatty change with degeneration of the protoplasm before that of the nucleus Glycogen disappears from the cells which may show bile pigment or disintegrate The bile capillaries are described as obstructed and there may be some interstitial change in the portal spaces, so that, if recovery occurs, cirrhosis may follow The spleen is usually enlarged

Pathogeny

According to Wells, phosphorus kills the liver cells but not their autolytic ferments and so extensive autolysis occurs As a result, hepatic inadequacy follows with the products of autolysis, leucin, tyrosin, cystin, sarcolactic acid, in the blood

Clinical Picture

The irritant effect of phosphorus on the alimentary canal supervenes a few minutes after the poison is taken in a soluble form such as phosphorated oil, but is delayed for three hours or so when it is taken in a solid form Vomiting, pain and collapse occur The vomit often contains blood and may be luminous in the dark The symptoms may prove fatal, or under treatment recovery may take place but in most of the cases after two or more days, severe symptoms, pointing to hepatic change are ushered in by return of grumous vomiting hepatic and splenic enlargement, hemorrhages and usually but not invariably by jaundice Prostration and coma follow and death occurs in two or three days The urine is somewhat diminished, highly colored, strongly acid, usually contains bile pigment and salts albumin, albumose casts, leucin and tyrosin and often acetone diacetic and sarcolactic acids, but very rarely sugar The total nitrogen is increased from autolysis of the hepatic cells which provides the leucin, tyrosin and albumose As a result of acidosis the urea is diminished and the ammonia increased The blood may show an increased red count, the

coagulation time is prolonged and its fat content increased Usually there is little or no fever The outlook is extremely grave

Diagnosis

The history that phosphorus has been taken is important, but in its absence the occurrence of severe gastric symptoms before the appearance of jaundice is suggestive The diagnosis from acute necrosis has already been discussed The condition in its later stages is like that produced by iodoform or delayed chloroform poisoning

Treatment

If the patient is seen soon after the poison has been taken the stomach should be washed out with a solution of permanganate of potassium (0 5 to 2 per cent) or peroxide of hydrogen (1 to 3 per cent) or sulphate of copper to form the comparatively harmless oxides of phosphorus Old French or oxidized oil of turpentine 40 minims (3 c c) in an emulsion should be given four times in the first hour and three times daily afterwards The bowels should be opened but castor oil and all fats which render phosphorus soluble should be avoided The treatment for the grave symptoms of the second stage is the same as in acute necrosis

3 HEMOLYTIC JAUNDICE

Hemolytic jaundice is a dissociated icterus with an increased bilirubin content of the blood serum without any corresponding increase of the bile salts and cholesterol or as in the phrase of the French school a pure pigmentary cholemia When from excessive hemolysis bilirubin is formed by the reticulo-endothelial cells in quantities too large for the polygonal cells of the liver to deal with some of the bilirubin passes straight into the hepatic blood vessels and causes jaundice while that acted upon by the polygonal cells escapes into the intestine and colors the feces

In true hemolytic jaundice the bilirubin content of the blood never equal that in obstructive icterus the blood serum gives a negative or delayed direct reaction with Hijmans v d Bergh s test bile pigment does not appear in the urine so that the condition is often called acholuric jaundice and the jaundice is never deep or black The icterus is an incident of an underlying process such as infection intoxication or metabolic error and does not of itself give rise to symptoms

Hemolytic jaundice may be acute in grave hemolysis such as that accom

panying paroxysmal hemoglobinuria, black water fever, snake bite, and severe infections and poisoning by chlorate of potassium, there may thus be overlapping with some forms of toxic and infective hepatic jaundice But the most characteristic form is chronic, and constitutes a definite clinical entity, of interest not alone from the point of view of diagnosis but from that of its treatment by splenectomy

Chronic Hemolytic (Acholuric) Jaundice

Definition A disease of the blood forming organs, in which chronic non obstructive jaundice is an obvious sign It presents microcytic anemia with exacerbations abnormal fragility of the erythrocytes, splenomegaly, but little or no hepatic enlargement, urobilinuria but not biliuria, normally colored feces, there is not any biliary toxemia

Etiology

Two forms are usually described (1) the congenital, hereditary or familial and (2) the acquired but the distinction between them is open to doubt, Gaensslen[69] put forward a hemolytic constitution with compensated cases without anemia (35 per cent including 5 per cent with polycythemia), jaundice (40 per cent) or splenomegaly (30 per cent), which may transmit the disease, and account for the cases regarded as acquired' On the other hand cases of chronic hemolytic anemia with jaundice of a quite different character have unfortunately been included in this group The condition may be congenital but not hereditary hereditary but not appearing until a considerable time after birth It has been known to come on after birth in one generation and to be congenital in the next generation This anticipation suggests that the process becomes intensified The blood changes may be present and transmitted by persons in whom the condition is latent, it is inherited as a dominant Mendelian character (Campbell and Warner[66]) The acquired disease may arise without obvious cause or come on after some acute infection

Pathogeny

The important feature is the diminished resistance of the red blood corpuscles and their liability to undergo hemolysis The cause of this fragility is not known It is not entirely due to the spleen, for it persists after splenectomy But the improvement that follows splenectomy is compatible with the view that the jaundice is due to overactivity of the reticulo-endothelial system The fragility has been ascribed to insufficiency of the bone marrow or to some in

herent vice of metabolism The hemolysis is not due to a hemolysin in the blood though the group of cases of jaundice with a hemolysin in the blood clinically resemble hemolytic jaundice

Morbid Anatomy

The extrahepatic and intrahepatic bile ducts are free from inflammation and obstruction Microscopically the small bile ducts are not blocked and there is no evidence of increased viscosity of the bile According to W J Mayo[67] 60 per cent of the patients even the very young have pigment calculi They may be numerous and are more often present in the congenital than in the acquired form The spleen weighing 1000 to 1500 gm is a dark purplish red and homogeneous on section According to Rich[68] and Thompson[69] the histological appearances are quite characteristic the Malpighian bodies are small and widely separated the blood sinuses dilated and their lining cells prominent and the pulp a mass of closely packed red cells The bone marrow is hyperplastic and in rare instances extra medullary erythroblastic foci have been found (Rich Dawson[70]) The cells of the retico-endothelial system show phagocytosis of the red cells and pigmentation

The blood in the hereditary and congenital cases shows abnormal fragility namely diminished resistance to hemolysis of the red blood cells when exposed to hypotonic salt solutions (Chauffard[71]) Normally this hemolysis begins in 0 42 per cent NaCl solution and is completed in 0 3 per cent solution whereas in hemolytic jaundice the corresponding limits are 0 6 and 0 42 per cent The red corpuscles are smaller than normal 6 microns instead of 7 5 microns and when stained show basophilia and usually polychromatophilia The number of reticulocytes is increased by 10 per cent or more The color index is about one Grave anemia has occurred later in cases with comparatively slight jaundice in early life (Dawson) The icterus index is not so high as in obstructive jaundice the blood serum shows a diminished cholesterol content and van den Bergh s test gives a delayed or negative direct reaction The leucocyte count is usually normal though a few myelocytes may be present during the crises a neutrophil leucocytosis and an increase in the myelocytes may occur In the acquired form the jaundice is less and the anemia much more prominent than in the congenital form

Clinical Picture

First described clinically by Claude Wilson [1] (1890) and Minkowski [2] (1900) the characteristic blood changes were established by Chauffard in 1907 In the hereditary congenital or familial form the jaundice may be the sole ab-

normal feature and the subjects are usually free from symptoms of chronic jaundice, such as itching xanthoma, clubbed fingers, and toxemia There is no arrest of growth such as is seen in the juvenile type of chronic hypertrophic biliary (Hanot s) cirrhosis, and the condition is compatible with long life, up to seventy The most striking symptoms are the occurrence of exacerbations of the jaundice and anemia which run parallel and in some instances, of febrile attacks suggesting biliary colic and associated with pigment calculi in the gall bladder These attacks are accompanied by drowsiness and increase in the size of the spleen The jaundice is increased after excitement, excessive exertion and exposure to cold and wet and symptoms are therefore more likely to arise in the winter The urine is high colored usually contains urobilin, but is free from bile except perhaps during exacerbations and as the result of complications it may contain hemosiderin free or intracellular (Rous[74]) Four cases showing spontaneous hemoglobinuria have been collected by Giffin[7] The spleen is enlarged in the vast majority of cases and more so than in the acquired disease its size increases during the exacerbations, when it becomes tender and the liver may be temporarily palpable

In the acquired form which is rarer than the congenital and commonly attacks young females jaundice usually comes on suddenly The spleen is less enlarged the anemia is much more pronounced and in addition the patients may suffer from febrile biliary colic although the jaundice is less than in the congenital cases Crises of hemolysis may occur and the condition may imitate pernicious anemia or cholelithiasis

From pernicious anemia in which the resistance of the red blood corpuscles is increased a diagnosis should be made by estimation of the resistance of the red blood cells to hypotonic salt solutions This test and the absence of hepatic enlargement should distinguish the disease from Hanot s cirrhosis It must also be diagnosed from macrocytic hæmolytic anemia (Davidson [6])

Prognosis and Treatment

Prognosis is very good as regards life in the hereditary cases, but although they are not ill they never become quite normal unless the spleen be removed In the acquired cases a spontaneous cure may occur

In view of the bad effect of cold and wet, exposure should be avoided For anemia iron should be given, but arsenic appears to be without any beneficial influence For severe anemia rest in bed is advisable A diet rich in cholesterol such as eggs, has been found to do good Splenectomy is the surest means of obtaining a definite cure it was first recorded by Micheli in 1911, and, according to Norris and MacMillan[77] the operation mortality among 93 recorded cases of splenectomy was about 5 per cent in 1921 Among 49 cases operated

upon at the Mayo Clinic there were two operative deaths[67] Chabrot[78] (1932) estimates the average operative mortality between 6 and 7 per cent In the great majority of cases the jaundice disappears within two weeks but the fragility of the red cells is unchanged Short of this operation x rays to the spleen may be tried Parisot and Heully[79] reported benefit in two congenital cases but further experience has not justified reliance on this method of treatment

Jaundice in the New Born

The various forms of jaundice met with directly after birth may be divided into (A) the mild forms that recover and (B) the severe forms with a grave prognosis

Mild Forms of Jaundice in the New Born

1 *Icterus neonatorum* synonyms idiopathic simple or physiological jaundice It occurs in from thirty to eighty per cent of all infants and is stated to be more frequent in small and feeble infants in hospitals and among the poor The incidence is equal in the two sexes It has naturally been correlated with circulatory changes and hemolysis in connection with the polycythemia at birth but opinions are discordant Williamson[80] finding that there is a direct relationship between the iron content of the placenta and the bilirubinemia and the jaundice of the new born ascribed the jaundice to hemolysis fetal or maternal in the placenta Ylppo[81] from spectroscopic examination of the blood for bile pigments ascribes the jaundice to increased bile formation by the liver just before and after birth and its passage into the blood especially in premature infants according to Murray[82] the more blood the infant receives from the placenta the less likely is jaundice to follow others and recently Franklin[83] take exactly the opposite view Rich[0] (1930) ascribes the jaundice to temporary functional incapacity of the liver to deal with the increased amount of bilirubin due to hemolysis he points out that the liver is immature that dye tests show functional inadequacy and that jaundice is more frequent in immature infants Post mortem examination shows general bile staining of the body except the liver kidneys spleen and cerebral cortex The cerebrospinal fluid the lenticular and other nuclei in the brain (Kernikterus) and the costal cartilages all of which escape in ordinary jaundice, are bile stained The bile ducts are normal

Jaundice appears on the first or second rarely the third or fourth day i e before the infective form and lasts weeks The sclerotics may escape or be affected later than the skin In rare instances of prolonged duration the tem

porary teeth have been green There are no symptoms, the pulse, feces, urine, and temperature being normal, but the urine almost always shows cells containing bilirubin With van den Bergh s test the blood serum gives the reaction for hemolytic and not for obstructive jaundice, the amount of bilirubin being much increased The prognosis is cloudless and treatment is unnecessary

2 *Catarrhal or mild infectious jaundice* due to acute duodenitis is usually regarded as decidedly rare in the new born The symptoms are those not uncommonly seen in older children with slowing of the pulse The prognosis is good The patient should be kept warm, given plenty of water and minute doses of gray powder or calomel

Severe Forms of Jaundice of the New Born

1 *Jaundice due to definite obstruction or organic change* such as congenital obliteration of the bile ducts, syphilis of the liver, syphilitic stricture of the bile duct, and gallstones are dealt with elsewhere

2 *Severe forms of infective jaundice* in the newly born (icterus gravis neonatorum) are due to the entry of microorganisms through the umbilicus the skin from damage received during birth or the alimentary canal The cases may occur in epidemics and formerly umbilical infection raged in lying in hospitals bathing infants before the umbilicus is healed is a disposing factor In umbilical infection there is suppurative phlebitis but the navel does not always show obvious inflammation The forms known as Buhl s disease (acute fatty degeneration) and Winckel s disease (afebrile cyanosis, jaundice and hemoglobinuria) are general septicemias probably of intestinal origin The morbid changes and symptoms in all these severe cases are much the same The viscera show the changes caused by septicemia or pyemia, such as cloudy swelling abscesses and bronchopneumonia

Clinically jaundice appears about the fifth day of life, and the skin is often bronzed from the combined icterus and cyanosis High fever with steep oscillations, rapid pulse and respirations hemorrhages such as hematuria, vomiting, and diarrhea restlessness passing into coma before death, which may be due to umbilical or gastrointestinal hemorrhage make up the clinical picture

Treatment — Antistreptococcic serum may be tried, especially in cases of umbilical infection The bowels should be washed out by enemas or purgatives and minute doses of calomel given frequently to act as a disinfectant in cases of probable intestinal infection

3 *Grave Familial Jaundice* — In this condition successive infants are born with jaundice or more often become jaundiced soon after birth and may die According to Pfannenstiel[84] it is an intense form of the physiological icterus neonatorum Necropsy shows bile staining of the organs and of the lenticular

and other nuclei (Kernikterus) of the brain although the cortex is unaffected effusion into the serous cavities punctate hemorrhages into the viscera and enlargement of the liver and spleen but no gross lesion to account for the jaundice There is no evidence that syphilis plays any part in this jaundice Usually the parents are healthy but in the families recorded by Nason[85] Tylecote[86] and myself[87] the mother became jaundiced in recurrent pregnancies The jaundice is not dependent on receiving the mother s milk which in Nason s case was deeply bile stained In Tylecote s case the mother remained jaundiced with a large liver after her eighth pregnancy and had xanthoma multiplex In several of the recorded cases the number of children was large and the first born has escaped It has occurred in twins The jaundice is usually noticed a few hours or days after birth The infants become drowsy and may die in convulsions The prognosis is bad out of 130 jaundiced infants 100 or 77 per cent. died but since then intra muscular injection of the mother s blood serum has given excellent results (Hampson[88]) Recovery after prolonged drowsiness is more often seen in the earlier members of an affected family When recovery occurs, it is usually complete but rare sequelæ are green teeth spastic diplegia and mental deficiency As a prophylactic measure the pregnant mother may be given hexamethylamin salicylate of sodium small doses of calomel 1/ o gr (0 003 gm) and a lacto-vegetarian diet

Latent Jaundice

Normally the blood serum contains bilirubin giving the indirect reaction in quantitie between 1 in 400 000 and 1 in 100 000 and van den Bergh takes 1 in 200 000 as the unit It is only when the bilirubin content of the blood reaches about 4 units (1 in 50 000) that bile appears in the urine The bilirubin content of the blood may thus rise so as to stain the skin but not appear in the urine this acholuric jaundice occurs in some sallow persons otherwise normal and in the allied if not identical condition called family cholæmia This latent jaundice also occurs in disease and especially in hemolysis and has been called urobilin jaundice it is present in pernicious anemia and often in cirrhosis It is al o seen in degeneration of the liver cells and its detection in patients under going salvarsan treatment is a danger signal

False and Feigned Jaundice

The skin of workers ır trinitrotoluene is stained yellow but not the conjunctivæ the feces are normal and the urine free from bile Picric acid in rare cases is absorbed from applications to burns and causes a yellow tinge of the blood plasma and so of the skin and mucous membranes Malingerers have

been known to paint the skin with saffron or tumeric, but the conjunctivæ are free from bile During the European War there was much picric acid jaundice, in fact epidemics of it occurred Some malingerers kept up chronic picric acid jaundice for five to fourteen months by taking picric acid from time to time (Marie[89]), 5 to 10 gr (0 3 to 0 6 gm) taken internally stain the skin and conjunctivæ for a week or two, the blood plasma is yellow instead of green as in true jaundice, and the urine, which is pomegranate red is free from bile but contains picramic acid Larger doses of picric acid cause diarrhea and vomiting Susceptible persons and those who have taken a large dose may get true jaundice about eight days later from damage to the hepatic cells Thus among 129 cases of picric acid jaundice Malmejac and Lioust[90] found biliuria in 7 per cent that picric acid can produce very serious damage is shown by Pauly's case[57] of acute necrosis due to melinite which contains picric acid The presence of bile does not interfere with the detection of picramic acid in the urine

Hess and Myers[91] under the term carotinemia described yellowish discoloration of the skin without involvement of the sclera due to carotin, a constituent of most vegetables of the diet Aurantiasis, a similar condition, may result from excessive consumption of oranges (Miyaka[9]) The urine as well as the serum is colored yellow Diabetics on a high fat diet may show a yellowish color to the skin

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CHAPTER VI

DISEASES OF THE LIVER (Continued)

By SIR HUMPHRY ROLLESTON

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Anatomical Abnormalities of the Liver

Various abnormalities of the liver congenital or acquired are encountered such as absence or excess of lobulation so-called accessory liver transposition ectopia furrows and corset liver These are of very slight practical clinical importance

Constriction lobes are sometimes painful but usually they are associated with rather than the cause of symptoms such as dyspepsia and gallstone manifestation They are often discovered during routine examination and familiarity with their clinical characters is important so as to avoid confusion with various abdominal tumors such as a floating kidney which indeed may also be present a growth of the pylorus of the hepatic flexure of the colon or of the right adrenal a dilated gall bladder cysts of the mesentery or pancreas a hydronephrosis an ovarian cystadenoma or a uterine fibromyoma

Treatment is mainly directed to the prevention of tight lacing a straight front corset should be substituted for stays that tend to constrict the waist and depress the liver When the site of much pain or in the very rare event of torsion (Tasca [1]) a constriction or pedunculated lobe has been excised but this is not often necessary

Acquired Displacements of the Liver

As a rule abdominal conditions such as ascites and tympanitic distention displace the liver upwards Thus ovarian cysts have been known to push the liver up so that its convexity was on a level with the third rib In cases of extreme abdominal distention the liver may move upwards and backwards on a transverse axis running through the inferior vena cava so that its anterior surface looks backwards and upwards and ceases to be in contact with the anterior abdominal wall Coils of intestine may intervene between the abdominal wall

and the liver and displace it backwards so that the hepatic dullness diminishes or disappears this occurs in acute yellow atrophy from the flaccid condition of the organ and in perforative peritonitis free gas may act in a similar manner A retroperitoneal growth or aneurysm may displace the liver forwards and give the impression that it is progressively increasing in size An abscess between the diaphragm and the convexity of the liver, or adhesions between the appendix or tuberculous glands on the one hand and the liver on the other hand, may cause downward displacement of the organ

Thoracic conditions such as a right sided pneumothorax or a large pleuritic effusion may displace the right lobe of the liver and tilt the left lobe A large pericardial effusion or a left sided pneumothorax may push the left lobe of the liver downwards An exceptionally large malignant growth of the lung may also depress the liver Traumatic rupture of the diaphragm which usually occurs on the left side, may allow the left lobe to enter the thorax, and I have seen the herniated part of the liver strangulated where it passed through the ruptured diaphragm In spinal curvature and in rickets the liver may be displaced and appear unduly prominent and enlarged A displaced liver is not more movable than in health and so differs from a wandering liver As a liver, which is really only displaced may be thought to be pathologically enlarged, a patient suspected of having malignant disease should always be carefully examined so as to detect any cause of displacement

Hepatoptosis

Synonyms —Wandering liver, movable liver Ptosis of the liver is part of general splanchnoptosis which is due to relaxation of the abdominal wall resulting from expansion of the linea alba and loss of reflex tone in the muscles (Keith) but from its intimate attachment to the diaphragm the liver is less often ptosed than other abdominal organs In addition to the dropping the liver is more movable than normal from relaxation of its suspensory and other ligaments as the result of malnutrition There does not appear to be any proof that the suspensory ligaments are congenitally lengthened

Sex and Age —Hepatoptosis is generally considered to occur mainly in multiparous women with pendulous abdominal walls Glenard [3], who found this condition with increasing frequency in successive papers, eventually estimated its incidence at 25 per cent of the males and 15 per cent of the females thus reversing the usual opinion which he suggested was due to the erroneous inclusion of cases with constriction lobes only But in Ssaweljew s [4] 117 collected cases 103 were in women, 13 in men and 1 in a child As a rule the patients are over forty years of age but among 496 necropsies on children Freeman [5] found 4 cases

Morbid Anatomy —In 1903 J Dutton Steele [6] estimated that 44 cases of hepatoptosis had been confirmed by laparotomy or necropsy An obvi

ously movable liver may from distention of the intestines and ascent of the diaphragm appear to be in its normal condition after death The ptosed liver is either simply anteverted from rotation on its transverse axis or in addition rotated on its vertical axis and usually to the right so that the convexity looks to the right The liver is elongated and flattened out and its anterior surface nearly always shows a transverse band of atrophy from tight lacing

Clinical Picture — Usually the onset is gradual but in about five per cent it is sudden suggesting dislocation In addition to the ordinary manifestations of splanchnoptosis there is a movable tumor which is firm smooth and dull on percussion to the right of the umbilicus The right hypochondrium is sunken and allows the hand to be passed over the surface of the liver which can be put back into its normal position when the patient lies down but falls two or more inches in a downward direction when he stands up the umbilicus becoming hidden from traction exerted by the falciform ligament The patient should therefore be examined both in the erect and recumbent postures The liver may be visible through the abdominal walls

The symptoms may be grouped as follows (1) hepatic pain or discomfort in the right hypochondrium radiating to the right shoulder and the neck relieved by the recumbent position (2) attacks of colic are frequent they occurred in 37 or 84 per cent of J Dutton Steele s 44 cases and were accompanied by jaundice in 14 or 31 8 per cent The attacks may be due to kinking of the bile ducts though kinking of the cystic duct would not cause jaundice torsion of the common bile duct would and in 15 cases with colic and transient jaundice gallstones were absent the torsion of the bile ducts might be due either to the movement of the liver or to the presence of a floating right kidney In 10 of J Dutton Steele s 37 cases of colic and jaundice gallstones were present (3) very exceptionally twisting of the portal vein produces gastrointestinal hemorrhage and ascites (4) gastrointestinal symptoms such as nausea vomiting and mucous colitis are common but may be due to the general splanchnoptosis (5) dyspnea and cough have been reported in some instances[8] There may be a complete absence of symptoms

Diagnosis — A constriction lobe is sometimes so large as to simulate a wandering liver but a constriction lobe though movable cannot be put into the position of a normal liver A floating kidney being much the commoner is often confused with hepatoptosis and the two may coexist and the distended gall bladder of a wandering liver may imitate a hydronephrosis The tumor should be carefully examined bimanually if necessary under a general anesthetic an attempt to put it into the right loin should be made and the hepatic region should be percussed in hepatoptosis the hepatic dullness is absent from its normal position and displaced downwards The same procedure may be useful in distinguishing a wandering liver from abdominal tumors and an X ray examination should give valuable assistance The diagnosis of an attack of colic due to torsion of the bile ducts from gallstones is difficult as gallstones

not infrequently are present in hepatoptosis If the attacks occur when the liver is kept in place, their nature is probably cholelithic

Prognosis is good as regards life and an efficient support should relieve the symptoms

Treatment — As a prophylactic measure, adequate rest in bed after parturition is important to enable the abdominal muscles to regain their tone Corsets which displace the liver downwards should be forbidden and a belt with a kidney pad substituted, but it is most important to improve the tone of the adbominal muscles by simple and carefully planned exercises and by judicious massage The general nutrition should be improved, the thin given nourishing food, the obese dieted on appropriate lines, and the general symptoms of splanchnoptosis attended to Gymnastic exercises and "walking on all fours" are recommended by Meunier [6a] and Hurst [b] If these palliative measures fail, operative fixation of the liver (hepatopexy) should be considered good results have been reported by Terrier and Auvray [7], Cernezzi and Rovsing, but as the patients practically always have splanchnoptosis the treatment is not perhaps so radical or successful as might at first appear

Functional Disorders of the Liver

The liver has such extremely important functions in connection with metabolism that it is desirable to have some idea of the results due to their derangement This may be indicated by briefly referring to the various functions of the liver

1 Secretion of bile The bile salts are manufactured solely by the liver cells, but it is still uncertain if bilirubin in any considerable amount is manufactured out of hemoglobin by the reticulo endothelial cells outside the liver The hemoglobin is first transformed by Kupffer's cells in the liver into bilirubin, which is then modified by the polygonal hepatic cells these two phases of bilirubin being those described by Hijmans v d Bergh [8] in hemolytic and obstructive jaundice respectively The bile salts play an important part in the digestion of fats and may exert an antiseptic action and inhibit bacterial growth in the intestine Bile pigment appears to be an excretion, except that it conserves the iron content of the body through reabsorption from the alimentary canal It was formerly thought that the secretion of bile could be arrested by various factors, and, although the grounds for this opinion were insufficient, it would appear from the analogy of toxic anuria that this event is not improbable It has also been thought that in mechanical obstruction of the ducts the secretion of bile may be diminished or arrested when the pressure reaches a certain point (Oertel [9], Blankenhorn [10]) Observations on biliary fistulae support the view that nervous influences modify the secretion of the bile which like the pancreatic juice, is stimulated by secretin liberated when HCl passes into the duodenum The vitaminic extract of brewer's yeast has been shown to stimulate

biliary secretion in the same way as secretin does (Wegelin and Meyer) By estimation of the concentration of the several constituents of the bile as obtained from the duodenum (McClure and Vance) further light may be thrown on the activity of the liver in the secretion of bile in various conditions there is some evidence that magnesium sulphate introduced into the duodenum stimulates the liver to increased secretion of bile quite apart from relaxing Oddi s sphincter

The secretion of bile by the liver cells may be distributed in various ways Instead of passing normally into the bile capillaries both the bile pigment and the bile salts may be shunted into the general circulation and cause complete jaundice This is admittedly the course of events in gross obstruction of the ducts but in a number of cases there is no obvious obstruction, even in the small bile ducts where however it has usually been assumed to be and in these cases there is often dissociated jaundice namely one only of these constituents usually the pigment is shunted into the blood while the other commonly the bile salts passes into the intestine This dissociated jaundice is an argument in favor of partial disturbance of the functional activity of the hepatic cells and has been produced experimentally by the injection of hepatocytolytic serum (Brule and Lemierre [2]) As long as the bile salts pass into the intestine the digestion of fat continues and this can be determined by Brule and Lemierre s blood test examination of the blood by the ultra microscope one and a half hours after a meal will if fat is being absorbed show the presence of hemoconia or minute particles of fat whereas in the absence of bile salts in the intestine as in complete obstructive jaundice they are absent from the blood If from functional disturbance the hepatic cells fail to secrete cholalate of sodium into the bile the normal solvent of cholesterol is diminished or absent and precipitation of cholesterol is prone to occur The existence of dissociated jaundice supports the contention that jaundice may be due to functional disturbance of the liver cells and that the constituents of the bile are extruded into the circulation instead of into the bile canaliculi This functional disturbance can be produced by poisons but it is not known if it can be caused by purely nervous influences and so in other words explain some cases of emotional jaundice Van den Bergh s [3] reaction by showing latent jaundice in cases of syphilis treated by arsphenamin has been found to provide information of degenerative changes in the liver and so of value in regard to further treatment (Gerrard) Piersol and Bockus [4] found the same evidence in these cases by using Rosenthal s modification of the phenoltetrachlorphthalein test as did Spence and Brett [5] with the levulose blood test

2 The formation storage and hydrolysis of glycogen is such an outstanding function of the liver that it is remarkable how rarely glycosuria occurs in cases in which the hepatic cells are widely degenerated or destroyed such as cirrhosis new growth and acute necrosis (yellow atrophy) Estimation of sugar tolerance by urinalysis after ingestion of sugar is unsatisfactory Bergmark and

MacLean and de Wesselow[17] showed that levulose is the only sugar which does not raise the blood sugar and as the liver is the only part of the body which can deal with levulose, the blood sugar content after the ingestion of 50 gms of levulose becomes a measure of liver function, a rise indicating that the liver is not functioning

3 The storage of fat by the liver is not so important in man as in animals, but in pathological conditions an increase in the fat content, which corresponds with a fall in the glycogen content of the organ may be associated with impairment of the functional activity of the liver cells, and simultaneously the disturbance of fat metabolism may give rise to acidosis According to J B Leathes[18] the liver cells alter the fatty acids brought to it by a process of desaturation and prepare them for further metabolism In hepatic disease the blood lipase normally very constant in amount, is increased

4 The part played by the liver in the metabolism of proteins is difficult to define The liver is certainly concerned in the conversion of ammonia into urea but there is no good evidence that it plays an important part in the manufacture of uric acid and there is nothing to support the assumption underlying Murchison s[19] conception of lithemia that in hepatic insufficiency uric acid instead of urea is produced in the liver In grave hepatic disease with destruction of the liver cells, such as acute yellow atrophy, phosphorus poisoning, some cases of cirrhosis and fatty change the amount of urea in the urine diminishes and that of ammonia increases this is not due to failure of the liver cells to form urea but to concomitant acidosis which entails linkage of the ammonia salts to fatty acids before the former can be transformed by the liver into urea It is only in the latest stages of these diseases that the liver cells lose the power of converting ammonia into urea In these cases the appearance of leucin and tyrosin is the outcome of autolysis of the liver cells, but Stadie and Van Slyke (1920) bring forward evidence to show that their excretion in the urine is due to failure of the liver to de aminize the amino acids and that even in the synthesis of urea the liver plays a part which cannot be entirely assumed by the rest of the body The liver is thought to be the chief source of fibrinogen (Foster and Whipple [20]) and when the hepatic cells are widely destroyed the fibrogen content of the blood falls (McLester, Davidson and Frazier [21]) the hemorrhagic tendency in grave hepatic disorders is thus explained Chronic inefficiency of the liver to deal with the metabolism of proteins has naturally been assumed to be a cause of high blood pressure and Sir Clifford Allbutt in his posthumous work on Arteriosclerosis (1925) accepted the possibility of the formation or imperfect destruction of a pressor amine

5 The detoxicating function of the liver normally prevents poisons taken into the alimentary canal or manufactured there from food especially proteins from exerting the effect that they would produce if introduced into the general circulation This is illustrated by the difference between the effects of strychnin and morphin when injected hypodermically and into the portal vein

(G H Roger) The effect of failure of the detoxicating function is prominently seen in structural diseases of the liver especially in cirrhosis and acute yellow atrophy by the appearance of drowsiness, coma, widespread hemorrhages the symptoms of this hepatic toxemia are comparable to those of uremia

The detoxicating function of the liver is impaired in obstructive jaundice in which icteric necrosis of the hepatic cells occurs, and in conditions in which the glycogen content of the liver falls Obvious failure of the antitoxic function of the liver is seen in cases of deep jaundice but the clinical manifestations often called cholemia depend more on the poisons that have passed through the liver than on the bile in the circulation The liver normally arrests poisons such as the aromatic products of putrefaction indol skatol and phenol formed in the alimentary canal, and transforms them into less toxic bodies thus indol becomes the indoxyl potassium sulphate or indican of the urine Kahn has elaborated a test for the efficiency of the detoxicating function of the liver on these lines thymol (0 5 gms) is given in olive oil to facilitate its absorption and the urine examined since if the function be normal there is a great increase in the ethereal sulphates whereas with failure of the detoxicating function there is little or no change in the excretion of ethereal sulphates Widal s[2] hemoclasic crisis test which consists in the absence of the usual leucocytosis after a meal a fall of blood pres ure and other changes, has been much discussed as evidence of hepatic insufficiency A positive result is ascribed to the entrance of incompletely metabolized proteins into the general circulation and so points to failure of the antitoxic function of the liver Tests for the estimation of the antitoxic function have also been employed depending on the absence of glycuronic acid in the urine when the liver is damaged after the ingestion or injection hypodermically of camphor (Roger and Chiray) or of 0 5 gr of sodium salicylate (Roch [3])

Functional disorder of the liver is responsible for many symptoms but the difficulty in regard to the subject is to prove that the functional manifestations are due to a primary insufficiency of the liver and not secondary to disease or extrinsic factors such as intestinal toxemia or dietetic indiscretions In popular parlance ' torpid or inactive liver and biliousness are so frequently employed that the current professional opinion is perhaps rather too adverse to admit any such possibility The popular incrimination of the liver as the cause of many symptoms more accurately ascribed to self indulgence in food and drink to constipation gout and idiosyncrasies is probably only the echo of the opinion of a past generation of physicians Lithemia was described by Murchison as a condition of innate defect of power, often hereditary of the liver which was therefore liable to be deranged by the most ordinary articles of diet As a result uric acid instead of urea was stated to be produced in the liver and turned out into the blood and dyspepsia constipation gout urinary and biliary calculi and acute and chronic renal disea e followed This hypothesis

is interesting only historically, and Glenard's [4] revival of it in 1899 under the name of hepatism with its cholemic and uricemic forms has been almost forgotten

Tests for Hepatic Efficiency

Numerous tests have been employed to determine whether or not the liver is functionally adequate At present these are being investigated in many clinics It is generally believed that tests of hepatic function add valuable information in regard to liver activity, but critical analysis of results up to date scarcely justify definite statements as to their real value in diagnosis, prognosis and treatment On the whole, they are now more helpful in diagnosis than in prognosis and treatment, but it is in prognosis and as a measure of the efficiency of therapeutic measures that they would be most useful to the clinician

Some of these tests have been mentioned incidentally in the discussion of functional disorders of the liver in the pages just preceding this section The more important tests, now under study, are dependent on several different principles Certain dyestuffs are quite specifically excreted by the liver and their amount may be measured in stools or duodenal content, or their rate of disappearance from the blood stream can be estimated, all by colorimetric methods Bile pigment excretion may be studied in various ways Bile salts, though methods still are unsatisfactory, can be determined in the blood stream or indirectly by methods that measure fat absorption etc Certain metabolic activities such as utilization of carbohydrates especially levulose [16, 17], can be studied by appropriate chemical technique Widal s hemoclasic crisis , fibrinogen e timations [0, 1] determinations of fibrinolytic ferment [5], nitrogen partition in the blood [6], blood lipoids the number of hemoconia granules in the blood [7] are other means that have been tried as a measure of hepatic activity A very good summary and critique of many of these tests will be found in a recent series of papers from the Mayo Clinic [8, 9, d 30]

However, it is obviously difficult, when an organ has a number of different activities, to arrive at a conclusion of value as to its all round efficiency by a test which is based mainly or entirely on one of its functions At the same time it must be admitted that such tests as we have are not specific enough to measure satisfactorily any of these several single functions More than one function may be impaired at the same time and so a test for any one may give positive results when another function is more obviously disordered This is a reason for the desirability of several types of test of liver function

Another difficulty lies in the inadequacy of our knowledge of the function of the normal liver Furthermore the very considerable reserve power of the liver and the occurrence of compensatory hyperplasia may preserve its functional efficiency so that very serious and extensive structural change may exist and yet the test for hepatic efficiency be normal Extensive destruction of the

liver in experimental animals may cause little change in the tests and the same slight results may be obtained in man from tests in such conditions as extensive multilobular cirrhosis gummatous changes or metastatic cancer in the liver It is indeed in acute cases of hepatic damage rather than in chronic disease in which there is time for hyperplasia of the liver cells to bring about compensation that efficiency tests give most striking results This may at times be misleading For example in the early stages of cirrhosis a test may show very poor function whereas in later stages when the lesion though established is not progressive or so active the test may give normal results although ordinary physical examination shows an obvious morbid condition of the organ

At the present time the tests depend on dyestuff excretion and those indicating variations in bile pigment in the blood stream would seem to have the greatest value Levulose utilization by some (MacLean and de Wesselow) is regarded as an extremely valuable measure of hepatic function while others question its value Of the various dyestuffs that have been used phenoltetrachlorphthalein [30] rose bengal [105, 31] azorubin S [32] and bromsulphalein the first appears to have the general preference particularly when used in the way suggested by Rosenthal [34] who determined its rate of disappearance from the blood stream Tetrachlorphthalein is a measure of general hepatic efficiency However Rosenthal s modification has been criticised from different aspects (Maurer and Gatewood [35] and others) Murphy [36] in the Medical Clinic of the Peter Bent Brigham Hospital has found that it gave little information not obtained from measurements of the bile index (as described on the next page) Large doses in animals can cause necrosis of the liver but this has little bearing on its clinical use where such doses are not used Unfortunately the test is not harmless and thrombosis has been reported to occur in 15 per cent of the cases [37] Were it easier to measure directly the amount of dyestuff excreted in the bile the test undoubtedly would be more valuable

Determinations of variations in the bile pigments of the blood serum are very helpful The presence of jaundice has ever been the most striking sign of disease of the biliary passages How much more efficient to measure bile pigment in the blood stream than to await its detectable accumulation in the skin sclerae or its excretion in the urine and in these places follow its variations Van den Bergh s test already referred to is a method of estimating the bilirubin in the blood and his direct and indirect delayed and diphasic reactions point to the occurrence of more than one form of bilirubin making possible a differentiation in types of jaundice obstructive toxic and hemolytic However there remains much that is unknown about the mechanism of the several forms of van den Bergh s reaction and we are not justified in being dogmatic in interpreting in a differential sense the various forms of jaundice Still the method is throwing valuable light on the problems of hepatic and biliary disease

The simple method of estimating the coloring matter of the blood serum by comparison with a bichromate solution the methods of Meulengracht usually

known as the bile index, values above six being regarded abnormal, helps much in the study of liver and biliary disease This comparison may be carried out in a colorimeter or more simply by means of a set of test tubes containing various dilutions of the bichromate solution, as suggested by Murphy[35] Of course this has the possible error of chromogenic substances other than bile pigment giving rise to an abnormal index, but on the whole this source of error is not a great one and in following variations in any given patient do not cause errors Murphy[6] has found that this very simple method yields results comparable in value to those obtained from Rosenthal's or van den Bergh's methods, though it scarcely can be said to be a method that should supplant them for after all, as already suggested, in an organ with so complex a function as the liver several methods of measuring functional efficiency will be needed It is evident that much more investigation is needed before satisfactory tests and their proper interpretation will be available

Symptoms of Functional Disorders

The symptoms formerly ascribed to functional disorders of the liver, such as distaste for food, flatulence intestinal disturbance mental depression and irritability headache, muscae volitantes, muddy and icteric conjunctivae, and pale stools can in most cases be reasonably referred to minor degrees of food poisoning or to dyspepsia, caused by unsuitable food, forming such an excess of toxic bodies that the liver cells are thereby affected, with the result that their functional activity is impaired From failure of this protective action poisons are able to pass into the circulation, while from disturbance of their biliary function some bile is shunted into the blood That there is functional disorder of the liver in these cases is clear, but it is secondary and not primary Symptoms of "torpid liver" are especially prone to occur in persons whose livers are already damaged, for example in the early stages of cirrhosis, in chronic venous engorgement, and in tropical liver Many so called 'bilious' attacks or indigestion especially in the young are really due to appendicitis, and may be accompanied by local tenderness, although there is no fever

That livers of different people vary like their brains and muscles, in their vigor must be true, but accurate knowledge of primary functional disease of the liver is wanting The symptoms of secondary hepatic disorder are, however, interesting as a field for investigation into the origin of structural disease of the liver, especially cirrhosis Although not satisfactorily proved, it would be unwise to deny the existence of primary functional disorder In the meanwhile the practical point is that primary insufficiency or disorder of the liver would require treatment possibly of a stimulating character, directed to the liver itself whereas in secondary hepatic disorder the treatment should of course be directed to the responsible cause

Treatment

Treatment of secondary functional disorders should be directed to removal of the cause in dyspepsia due to oral sepsis the teeth should be thoroughly attended to constipation should be corrected so as to obviate autointoxication and in all cases the diet should be carefully supervised restricted even to short fasts and idiosyncrasies considered, for example that to eggs Generally speaking the following articles of food should be avoided, concentrated and highly spiced soups made from stock condiments rich fish such as mullet salmon, eels, and kippered fish stews much meat melted butter sauces, duck, goose, hare sausages liver and bacon sweetbread entrees rich puddings cheese The diet should be simple and the amount of food taken should fall short of that necessary to give the sensation of full satisfaction Alcohol should be forbidden or, if this be impracticable taken in small quantities and well diluted and after meals Plenty of water or of alkaline mineral water such as Vichy should be taken before meals The bowels should be kept open, if necessary by salines, intestinal flatulence if not thus prevented may be restrained by minute doses of calomel 1/20 gr (0 003 gm) three times a day salol grs v (0 3 gm) in powder mixed up with a few grains of magnesium carbonate naphthalene tetra chloride grs vii (0 5 gm) twice daily or beta naphthol Active exercise should be encouraged the free action of the skin stimulated and a visit recommended to a spa such as Vichy Evian Brides Harrogate Llandrindod Wells Strath peffer Bedford Pa Las Vegas Hot Springs N M Greenbrier White Sulphur W Va, Ems and Neuenahr

During the presence of symptoms a bland vegetarian and mild diet or semistarvation with plenty of water should be enjoyed while the bowels are freely opened by the old fashioned blue pills grs v (0 3 gm) followed by senna mixture and constipation prevented by salines An alkaline mixture containing bicarbonate of sodium and small doses of sodium salicylate may be taken before food

Thrombosis of the Portal Vein

This condition also called pylethrombosis or pylephlebitis adhesiva may involve the whole or more often part of the portal vein and its branches it may be confined to its radicals in the mesenteric veins or to the intrahepatic branches

Portal thrombosis is due to various causes infection of a nonpyogenic nature accounts for some cases and other cases show a transition to suppurative pylephlebitis Chronic inflammation of the portal vein in some instances syphilitic or combined with hepatic syphilis may cause it But the most frequently associated conditions are portal cirrhosis and intra abdominal malignant disease Portal thrombosis however does not occur in more than three per cent of all the cases of cirrhosis among 275 fatal cases of cirrhosis at the Johns Hopkins

Hospital it was found in 7, or 2 6 per cent (Webster [39]) It is especially prone to be associated with multiple adenomas and cirrhosis Malignant disease of the liver especially primary carcinoma supervening in cirrhosis, may induce portal thrombosis by direct invasion of the intrahepatic branches The pressure exerted by malignant tumors on the trunk of the portal vein or its actual invasion may cause thrombosis In a few cases injury, puerperal eclampsia extension of thrombosis from the hepatic or splenic veins, or association with thrombosis in other parts of the body, may be invoked To cases without any obvious cause the name primary portal thrombosis has been applied

It occurs more often in males than in females and after forty years of age, thus corresponding fairly with the incidence of cirrhosis, among women intra abdominal malignant disease was responsible for a third and cirrhosis for a sixth of my sixty two cases, whereas half the male cases were due to cirrhosis

Morbid Anatomy —In recent thrombosis the portal vein is tensely distended with adherent clot, and the tributaries, such as the coronary and esophageal veins may be dilated, Pick's hepatopetal veins in the lesser omentum may still convey blood to the liver In old standing cases the portal vein may be shrunken to a fibrous cord and a collateral circulation highly developed Phlebosclerosis with calcification of the vein wall may be either the antecedent or the result of thrombosis When, as is often the case in portal thrombosis, the splenic vein is also blocked, the spleen becomes much enlarged and may contain infarcts The liver often shows the probable cause of portal thrombosis, namely, cirrhosis and multiple adenomas or malignant disease The hepatic artery is dilated as a compensatory measure but, from the impaired blood supply consequent on portal thrombosis, the hobnails or adenomas of a cirrhotic liver may undergo fatty and degenerative changes As a direct result of portal thrombosis the liver may show infarcts, usually hemorrhagic, and, from atrophy of the liver cells some fibrous replacement Experimentally Rous and Larimore [40] have shown that after obstruction of a branch of the portal vein the corresponding part of the liver undergoes simple atrophy provided compensatory hypertrophy of liver tissue elsewhere occurs, the atrophy is thus conditional on hypertrophy These experiments may explain the absence of universal atrophy of the liver cells in complete thrombosis of the portal vein

The *clinical picture* is determined (a) by the site and extent of the thrombosis and (b) the rate at which the vein is occluded Rapid thrombosis of the trunk of the portal vein causes hematemesis acute ascites and death whereas with gradual occlusion of the trunk of the vein, which allows time for the development of a collateral circulation the symptoms are those of chronic splenic anemia, namely splenomegaly, anemia of the chlorotic type with leukopenia, and periodic gastrointestinal hemorrhages In exceptional cases there has been polycythemia (Van der Weyde and Ijzeren [41]), eosinophilia, and a bruit in the epigastrium due to the collateral varices (Hatzieganu and Sharteu [4]) Acute thrombosis of the mesenteric veins gives rise to the symptoms of intestinal ob-

struction Jaundice is not directly due to portal thrombosis but it may be a concomitant result of its cause such as carcinoma of the liver or pancreas The urine is diminished alimentary glycosuria has been stated to be constant but this is very doubtful

Diagnosis is extremely difficult In a case known to have cirrhosis the acute onset of hematemesis and ascites might suggest it The sudden onset of ascites is not of much value as it may occur in cirrhosis e pecially when complicated by tuberculous peritonitis

Prognosis —With a sudden onset of symptoms the outlook is very bad though recovery sometimes occurs and the symptoms become those of chronic splenic anemia as in the cases with a gradual onset In the e circumstances life may be prolonged for many years but there is always the risk of gastrointestinal hemorrhage which may occur periodically or be suddenly precipitated by thrombosis of the compensatory collateral circulation

Treatment is unsatisfactory especially in acute cases In chronic cases the risk attending the Talma Morison operation for promoting vascular adhesions or splenectomy is very considerable on account of the free collateral circulation already developed

Suppurative Pylephlebitis

This infective inflammation of the portal vein or portal pyemia varies in extent it may occupy the whole extent of the vein be almost confined to its tributaries in the mesentery or to its terminal branches in the liver and in the latter event is much the same as the less rare condition of multiple abscesses due to embolism of the portal vein It is fortunately rare It is due to infection de rived from the area drained by the portal vein especially from abscesses under tension The most prolific source is appendicitis particularly neglected cases but it occurs in less than 1 per cent of all cases of appendicitis Among 2 714 cases of appendicitis in various London hospitals it was noted in 0 4 per cent and in the proportion of 0 25 per cent among 2 000 cases collected by Rendle Short [43] It may have started before the appendicectomy was performed In infants suppuration may spread from the umbilical vein Other causes are rare particularly ulcers of the stomach duodenum or intestines such as typhoid tuberculous dysenteric or malignant Suppuration in connection with the spleen pancreas gall bladder or diverticulities of the colon (pericolitis sinistra) may be the origin Direct penetration of the branches of the portal vein by fish bones or bristles may be the primary focus as may pelvic conditions such as pyosalpinx or operation for piles and in the liver itself suppurating hydatid cysts It is commoner in young males probably in correspondence with the incidence of appendicitis

The vein is distended with broken down clot or sanious pus which may ex tend into the adherent tissues and thus give rise to an abscess in the mesentery Rupture is very rare The liver is nearly always infected and enlarged even

inflammation of its capsule from the underlying abscesses is common, and there may be perihepatic or subphrenic abscesses as a further development On section there are numerous abscesses in the situation of the portal canals which may be dark green in color The abscesses may run together into a large cavity or form a honeycombed area resembling that of actinomycosis This change may be comparatively localized, for example at the back of the right lobe The left lobe, which has been thought to receive the blood from the stomach and spleen, not infrequently escapes Inflammation is prone to extend to the right pleura and in some instances pyemic abscesses outside the portal area occur as in the lungs and even in the brain As in pylethrombosis, the spleen is often enlarged partly from obstruction of the splenic vein, partly from toxic changes Streptococci, staphylococci, bacillus coli are the micro-organisms usually present, but bacilli of the typhoid and dysentery groups, entameba histolytica streptothrix and others have been recorded

Clinical Picture — The onset may be sudden or run into the symptoms of the causal lesion In a characteristic case there are first the symptoms of appendicitis then of a pyemic state ushered in by rigors, high fever, and grave constitutional state and lastly evidence that the liver is affected — enlargement, tenderness and sometimes jaundice The patient is and looks gravely ill with a rapid pulse (100–140) and respiration, leukocytosis, and repeated rigors Blood cultures are negative (Libman[44]), unless suppuration spreads to the hepatic veins Later tender enlargement of the liver in more than half and jaundice in less than half of the cases occur Diarrhea is seen in about half the cases Abdominal pain and distention are common The spleen may be palpably enlarged and peritonitis and right sided pleurisy supervene Ascites is rare Hiccough may be troublesome before the patient becomes stuporous and moribund

Prognosis is very grave In some cases which Quenu and Mathieu[45] collected recovery has followed operation with the evacuation of abscesses, but usually the abscesses are so numerous as to render this futile A few cases, suggesting that the process had become arrested, have been published

Diagnosis may be easy with the history of a recent infective focus such as appendicitis with pyemic symptoms, especially a rigor (Gerster[46] Thalhimer[4]) and a large tender liver In the absence of a suggestive history and of hepatic enlargement the diagnosis is very difficult and especially from suppurative cholangitis (under which heading the diagnosis is discussed) Typhoid fever, unless there is any complication would be ruled out by leucocytosis, and a negative agglutination reaction would have the same effect, infective endocarditis may give a positive blood culture which as has been mentioned does not occur in suppurative pylephlebitis in addition evidence of widespread arterial emboli cutaneous petechiae, retinal hemorrhages point to infective endocarditis In the absence of a primary focus the association of an enlarged liver and a septicopyemic state may suggest ordinary hepatic or subphrenic abscess syphil

itic liver, acute cirrhosis or be imitated by rapid malignant disease of the liver

Prophylaxis consists in early removal of a suppurative focus and ligature or possibly removal of thrombosed veins in the neighborhood

Treatment —The use of antistreptococcic serum is speculative Occasionally there are one or two abscesses and evacuation of these has been followed by recovery otherwise the prognosis is almost lethal Operation is justified and should consist in laporatomy exploration by a trocar through the abdominal wall is dangerous and should not be attempted Any pus obtained should be cultivated so that if necessary a vaccine can be employed A cure has followed the intravenous injection of eusol (Barlow [8]) Such antiseptics as gentian violet or mercurochrome deserve a trial used intravenously

Other Diseases of the Portal Vein

Embolism is common as a cause of secondary malignant disease and of multiple abscesses Embolism of uninfected clot or of clot containing nonpyogenic organisms may cause hepatic infarcts

Acute endophlebitis is part of pylephlebitis *Chronic endophlebitis* is seen in portal cirrhosis in syphilis with or without hepatic lesions in association with chronic venous engorgement of the liver and in chronic splenic anemia, especially in its further stage when hepatic cirrhosis has supervened or Banti s disease Calcification and dilatation are later results of endophlebitis and like it favor thrombosis A hemangioma has been known to arise in the vein and obstruct it

Diseases of the Hepatic Veins

Occlusion of the hepatic veins close to their junction with the inferior vena cava is due to various causes which may conveniently be tabulated under the headings of thrombosis and stricture though these two conditions may be combined or etiologically related

Thrombosis may result from the extension of new growth of the liver especially primary carcinoma in cirrhosis into the hepatic veins or from extension of thrombosis from the inferior vena cava an association recently insisted on by Nishigawa Several instances of such thrombosis due to renal or adrenal neoplasms are on record Infection of the liver for example in abscess may lead to thrombosis of the hepatic vein and in some instances the hepatic veins share in widespread thrombosis the junction with the inferior vena cava being perhaps a favorable site Portal thrombosis may appear to be the causal factor

Stricture may be caused by gummatous infiltration of the liver and extensive fibrosis in the neighborhood of the main hepatic veins It may be associated with cirrhosis The cases of primary obliterative endophlebitis of which

Schmidt[49] collected thirty examples, are somewhat difficult to separate from those in which the fibrotic process has started outside the vein Syphilis may account for some of the cases, others have been thought to be developmental, or to depend on excessive cicatrization following small tears of the walls of the veins (Kretz) and the process has been regarded as secondary to thrombosis a thrombophlebitis (Turnbull and Thompson [0]) The hepatic veins may be compressed by intrahepatic tumors or hydatid cysts The liver shows a high grade of chronic venous engorgement with dilatation of the trunks of the hepatic veins The Spigelian lobe may show curious enlargement (Hess[51])

The symptoms are those of severe chronic engorgement of the liver which is present in a high degree The disease may run a chronic course imitating chronic venous engorgement or cirrhosis, or it may be acute with the rapid onset of ascites followed by delirium, coma, and death in a few days The different clinical forms would correspond with stenosis and complete obstruction Sudden hepatic enlargement coinciding with the onset of acidosis in a patient with signs of obstruction of the inferior vena cava would be compatible with acute obstruction of the hepatic veins (Jacobson and Goodpasture)

Dilatation with some chronic but not obliterative endolphlebitis of the hepatic veins occurs in the backward pressure of chronic cardiac failure

Suppurative phlebitis of the hepatic veins may be secondary to suppuration in the liver and is prone to give rise to embolic abscesses in the lungs and so to general pyemia

Embolism of the hepatic veins can only be retrograde or occur when as the result of straining as in coughing, the blood stream is reversed and an embolus just passing the orifices of the hepatic veins is carried into them

Diseases of the Hepatic Artery

Aneurysm of the hepatic artery is rare Among Friedenwald and Tannenbaum's [3] 63 cases, males were affected nearly four times as often as females and had an average age of 36 as compared with 44 in females Infective embolism has been thought to be the most frequent cause but it is sometimes due to ulceration from without, caused by gallstones or even by an abscess or tuberculous glands Usually the trunk or extrahepatic branches of the artery are affected but in 18 cases the aneurysms have been intrahepatic, numerous small aneurysms may be found in the liver in periarteritis nodosa and especially in the allied condition of polyarteritis acuta nodosa (Dickson[54])

Clinically biliary colic and jaundice due to pressure on the bile ducts are common, fever occurs in a third of the cases tumor and pulsation are absent rupture commonly results (in 45 out of 65 cases into the peritoneum in 33, into the bile passages in 21) gastrointestinal hemorrhage occurred in 31 out of 49 cases blood is passed by the bowel when the aneurysm ruptures into the bile passages, and the condition is usually regarded as gallstones or duo

denal ulcer Very rarely, in two instances only has a correct diagno is ever been arrived at before the abdomen was opened Unless operated upon death is probably certain So far the operative results are ten operations with three recoveries

Embolism of the hepatic artery has been very seldom recorded, but it obviously must occur in multiple pyemic abscesses in generalized sarcoma and tuberculosis In a few cases embolism of a large branch has produced anemic necrotic infarcts of the liver The nearer to its bifurcation the artery is occluded the more likely is an infarct to result (Segall)

Thrombosis has been even more rarely reported *Arteriosclerosis* is occasionally seen in wide pread arterial disease and may dispose to aneurysm Endarteritis obliterans occurs in the neighborhood of gummas in hemochromatosis and occasionally in portal cirrhosis

Enlargement of the artery is seen in portal cirrhosis and sometimes in new growth of the liver

Chronic Venous Engorgement of the Liver

Venous engorgement may be acute as in cases of cardiac failure due to pneumonia or diphtheria in cases of quite recent paroxysmal tachycardia or auricular fibrillation or in cases of well compensated mitral disease with onset of cardiac failure shortly before death The liver then presents the first stage of the nutmeg liver of chronic venous engorgement In erythremia the blood vessels of the liver are all overdistended but this is quite different from the condition now under consideration

Chronic venous engorgement is the result of tricuspid regurgitation of considerable duration however produced especially by failure of compensation in mitral disease emphysema of the lungs pneumoconiosis and adherent pericardium though less important than mitral stenosis are well recognized causes Stenosis or occlusion of the hepatic veins usually produces a high degree of chronic venous engorgement and the pressure of intrahepatic tumors may cause localized areas of this change In the very rare instances of occlusion or thrombosis of the inferior vena cava between the openings of the hepatic veins and the pericardium the liver is nutmeggy

The surface of the organ may show old adhesions and some lines of depression due to the atrophy but it is smooth except when from long standing ascites the capsule is thickened and opaque In some cases from an acute terminal infection there are areas of acute perihepatitis The size of the liver varies usually somewhat larger than normal it becomes smaller as time goes on from atrophy and fibrous replacement

Clinical Picture — Usually the causal lesion such as mitral stenosis is obvious and the enlarged liver is merely an index of the degree of cardiac failure But in some cases which Hanot [a] termed hepatic asystole the liver symptoms

dominate the field These are enlargement, tenderness, ascites, dyspepsia and slight jaundice The enlargement, which is due to the sponge like liver compensating for the failing circulation by accommodating the excess of blood may vary rapidly with the condition of the heart thus it may come and go with the occurrence of auricular fibrillation The liver may be tender from distention and painful apart from palpation as the result of acute local perihepatitis, or the tenderness may, as Mackenzie pointed out, be really in the abdominal wall and more extensive than the area corresponding to the liver, and due to tenderness referred from the liver to the seventh to tenth dorsal skin areas the muscles being rigid as a mechanism of defence The surface of the liver is smooth In a small proportion of cases the liver can be easily felt to pulsate, and in a larger number the polygraph will reveal the presence of pulsation According to Mackenzie when this has once appeared it probably persists

Ascites is very common, and, like that of chronic universal perihepatitis, recurs again and again The subcutaneous abdominal veins are very seldom enlarged and the spleen, unless infarcts or infection complicate the case, is not palpable The urine is that of cardiac failure, but exceptionally leucin and tyrosin from autolytic destruction of the liver cells have been found Oertel[58] has described multiple aseptic necrosis of the liver cells in the center of the lobules with deep jaundice delirium and coma, as a terminal event Icterus gravis may also be infective and due to streptococci The icteric tint so commonly present may be ascribed to disturbances of the hepatic cells and the consequent shunting of the bile into the circulation instead of into the biliary canaliculi

Diagnosis — If the causal lesion be overlooked or not obvious, the large tender liver may be regarded as the site of new growth or abscess I have seen a case of this kind associated with malignant endocarditis operated upon and fatal hemorrhage result from puncture of the liver on the erroneous assumption of an abscess A case is known to one of the editors (H A C) in which the pulsating liver, associated with an unrecognized mitral stenosis, was mistaken for a pulsating neoplasm, and ligation was attempted

The treatment is that of the cause cardiac failure mainly For pain due to perihepatitis half a dozen leeches are most efficacious, hot applications such as poultices may be tried

Pericarditic Pseudo Cirrhosis

Pericarditic pseudo cirrhosis was described by Pick[59] in 1896 in patients with adherent pericardium The liver is in an advanced stage of chronic venous engorgement with fibrous hyperplasia but does not show chronic perihepatitis such as may be seen in association with adherent pericardium no doubt transitional cases occur, and Kelly[60] in fact, included Pick s disease in chronic universal perihepatitis But it seems to me right, in view of Pick s statement that

any peritoneal change is a secondary process to regard this group of cases as the same as chronic venous engorgement

The liver shows advanced changes of chronic venous engorgement with fibrous replacement especially under the capsule where to the naked eye the appearance suggests chronic thickening of the peritoneum but microscopic examination at once shows the difference The orifices of the hepatic veins are much dilated and the brunt of backward pressure falls much more on the hepatic veins than on the rest of the inferior vena cava so that the kidneys and lower limbs escape more or less from the effects of venous stasis Adherent pericardium is part of the disease in some instances it is tuberculous and then the liver also may be tuberculous These cases have been called cardio tuberculous cirrhosis but tuberculous peritonitis may supervene as a complication as was proved in a case of Nachod s in which a previous laparotomy had shown a healthy peritoneum

The clinical features described by Pick were recurrent ascites an enlarged firm liver absence of or slight jaundice and no edema of the feet The main clinical difference from ordinary nutmeg liver is the absence of evidence of cardiac valvular disease The treatment is that of chronic venous engorgement of the liver namely cardiac tonics diuretics and a dry diet Pick recommended the operation of cardiolysis

Acute Active Congestion of the Liver

As this is the earliest stage of acute hepatitis which may never go any further it is impossible to draw a hard and fast clinical distinction between them except by the temperature Cantlie [1] drawing the line at 100 F and Davidson [42] at 102° F

In temperate climates persons who have never been in the tropics are often seen to have attacks variously termed congestion of the liver biliousness or a chill on the liver In such patients over-eating excessive alcoholism and constipation are causal factors These cases might equally well come under the vague headings of functional disease of the liver or lithemia No doubt poisons are absorbed from the intestine and produce the general symptoms and the swelling of the liver when it can be made out But poisons brought by the hepatic artery can also cause congestion as in the acute infections Suppression of the menstrual flow and the stoppage of bleeding from piles are traditionally but probably with little reason supposed to cause acute hepatic congestion

Except in the acute fevers opportunities for examining the liver very seldom occur and it is rather doubtful if the morbid appearances are accurately known The liver is described as uniformly congested with cloudy swelling fatty change and pigmentary infiltration of the liver cells and proliferation of the epithelium of the small bile ducts when jaundice is present but the last change would point to the further stage of inflammation

The symptoms are malaise, headache, mental irritability and depression spots before the eyes, insomnia, loss of appetite, dirty mouth and tongue, tainted breath, nausea, flatulence, constipation or diarrhea, a feeling of fullness in the hepatic region, pain in the right shoulder, muddy or icteric conjunctivae, congestion of the face, occasionally epistaxis and piles The urine is high-colored uratic, and contains excess of urobilin and, when there is jaundice, bile pigment The liver may be enlarged and tender When treated, the condition should not last more than a week Acute congestion of the liver in persons who have never been out of temperate climates may be a polite paraphrase for the dyspepsia of gluttons or alcoholics, and the diagnosis of acute congestion is therefore only justified in the presence of a recent tender enlargement of the organ

In persons who have lived in the tropics and have had dysentery or malaria attacks of general malaise, slight fever, and tender hepatic enlargement are much more prone to occur than in those who have not been so predisposed The attacks may be precipitated by indiscretions in diet or by exposure to cold especially east winds When these attacks are frequently repeated the resulting condition is often called tropical liver, but it may well include cases of early cirrhosis or subacute hepatitis The liver may then be much enlarged, tender and firm, and the spleen especially when there is a history of past malaria, also palpably enlarged

Prophylaxis and Treatment

Prophylaxis consists in rational moderation in diet the avoidance of alcohol except in small quantities well diluted after meals, and of all highly spiced food Plenty of exercise should be enjoined and constipation corrected Care should be taken to avoid draughts, proper clothing should be insisted on, and the abdomen, the back of the neck and the feet and legs should be properly protected

Treatment should be much on the same lines as that for acute indigestion namely rest in bed, practical starvation for a few days, absolute teetotalism and free purgation with calomel or pilula hydrargyri grs 5 (0 3 gm) followed by salts Any suspicion of amebiasis demands a trial of emetin Ammonium chloride in 30 grain (1 3 gms) doses has been much recommended Pain in the hepatic region may be relieved by leeches hot compresses poultices, or a liver pack Aspiration of the liver though highly recommended, is not without risk of serious dangers from hemorrhage and should not be employed As the acute symptoms subside the diet may be increased gradually, but be kept on very simple lines and active exercise especially on horseback, is advantageous Benefit often follows a wisely supervised course at a spa such as Vichy, Brides Saratoga Harrogate Llandrindod Wells Acid tonics are often recommended but probably a combination of alkalis with nux vomica is as good or better

Acute Non Suppurative Hepatitis

As already mentioned acute congestion is the earliest stage of acute hepatitis and any hard and fast line of demarkation may be difficult or impossible Acute hepatitis is in like manner the precursor of hepatic suppuration and in amebic hepatitis prompt treatment with emetin is most important in arresting the process before suppuration has begun

Acute hepatitis presents several forms and is due to many causes It occurs in the acute infections and intoxications for example malaria dysentery scarlet fever influenza septicemia pyemia In typhoid fever puerperal eclampsia and in other infections focal necroses with sub equent small celled infiltration occur and hepatitis though mainly manifested by microscopical rather than by clinical examination is nearly always associated with cholecystitis and cholangitis either as cause or effect With the acute necrotic changes seen in trichlorethane and trinitrotoluene poisoning and in yellow atrophy there is also some acute inflammation It may be difficult to draw the line between subacute atrophy and special forms of hepatitis for example in that rare lesion acute parenchymatous hepatitis there is compensatory hyperplasia of the liver cells as in subacute atrophy

The morbid changes vary in the different forms and may be mainly parenchymatous or interstitial In evere malarial infection the liver is enlarged swollen and pigmented In the nodular parenchymatous hepatitis of malaria there are numerous nodules of hyperplasia of the liver cells resembling those in nodular cirrhosis and in subacute atrophy Microscopically there may be a diffuse hepatitis or the focal necroses of typhoid eclampsia and various infections The diffuse form shows acute congestion and in addition thrombosis of the small vessels acute lymphangitis and cholangitis and small celled infiltration of varying extent spreading out from the interlobular portal canals In severe malaria there are phagocytes containing parasites and pigment and pigmentation of the liver cells

The *clinical pi ture* is on the same lines as in acute congestion but the symptoms are more severe and jaundice when accompanied by well marked constitutional disturbance may present the features known as icterus gravis The pain in the right shoulder is more severe From extension of hepatitis to the diaphragm its movements are painful and as seen by the fluoroscope are restricted In amebic hepatitis leukocytosis without any polymorphonuclear increase is described by L Rogers [65] The temperature is higher and vomiting and gastrointestinal disturbances more prominent than in acute congestion The presuppurative amebic hepatitis may continue for weeks or even months

Diagnosis —When jaundice is present the distinction *from acute yellow atrophy depends on the presence of nervous symptoms in that disease and the diminution in the size of the liver which at first may be enlarged* Both in acute

atrophy and phosphorus poisoning the constitutional symptoms are more severe than in acute hepatitis With a large tender liver it may be difficult to exclude suppuration in amebic hepatitis there is, according to L Rogers a leukocytosis, but like that of amebic abscess with a relative lymphocytosis and thus differing from other forms of suppuration such as pylephlebitis Amebic hepatitis, especially when the original infection has been insufficiently treated may closely imitate typhoid fever (Boyd [4]), but agglutination reactions should help in the diagnosis

Prophylaxis is on the same lines as in acute congestion with the addition that cases of amebic dysentery should be thoroughly treated with emetin

Treatment — When amebic hepatitis is suspected, vigorous treatment by emetin bismuth iodide 3 grains (0 2 gm) daily until 36 grains (2 5 gms) have been taken is essential The treatment has superseded that of ipecacuanha and ammonium chloride and proved most satisfactory In other ways the treatment is on the same lines as in acute congestion and is symptomatic

Suppurative Hepatitis

It is convenient to divide suppurative hepatitis into (1) large abscesses usually but not always, single, and (2) multiple abscesses This however, does not include all the forms of hepatic suppuration a subphrenic abscess may erode and infiltrate the liver suppuration may spread into the liver diffusely from a necrosing carcinoma of the cardiac end of the stomach

Single or Tropical Liver Abscess

Large abscesses usually single, are often called tropical, but they also occur in temperate climates

Etiology

The great majority of large abscesses are amebic In a fair number of amebic abscesses there is no history of dysentery According to L Rogers [65] the large amebic abscesses are often secondary to latent amebic ulceration of the colon whereas extensive gangrenous amebic dysentery causes multiple small amebic abscesses in the liver, which may be latent during life he correlates these two forms with the advent to the liver of comparatively few and of very numerous entamabae respectively Amebiasis may occur in persons who have never been out of temperate climates and are presumably infected by a carrier Thus, among 504 recruits who had never been out of England but were in a camp containing men who had returned from the Mediterranean, Glynn [66] found that 24, or 4 8 per cent were amebic carriers This explains amebic abscesses in persons who have never been out of temperate climates Amebic abscesses

have been known to occur 20 (Low[*]) 29 (Durand[58]) and even 30 (Mallory[9]) years after an attack of dysentery Secondary microbic infection may complicate amebic hepatitis but is not essential for suppuration and L Rogers found the pus sterile in large amebic abscesses in 86 per cent of his cases

Bacillary dysentery is practically never followed by a large abscess unless as may easily happen a case which in its acute stage was due to a pure bacillary infection becomes complicated by amebiasis In campaigns for example in Manila during the Spanish American War and in Salonika during the Great War both infections may be rampant side by side

Other causes of large abscesses are relatively unimportant Trauma may act (1) by the direct introduction of pyogenic organisms into the liver e g a bullet knife or dagger wound exploratory puncture of an empyema may introduce pus into the liver and in rare instances a pin needle or fish bone penetrating the walls of the alimentary canal may enter the liver and thus give rise to an abscess (2) indirectly by reducing the resistance of the liver and so enabling microorganisms that happen to reach the liver either from the hepatic artery or from the portal vein to multiply In children injury has been thought to have a special etiological importance among 112 cases of intrahepatic suppuration in children 19 were ascribed to trauma (Legrand[9])

Typhoid fever like bacillary dysentery is very rarely followed by hepatic abscess In 1911 von Eberts collected 30 cases and in 1913 Preble estimated that B typhosus had been isolated in 12 cases only in 8 in pure culture and in 4 with streptococci or staphylococci The focal necroses commonly present in the liver in fatal typhoid fever must favor hepatic suppuration when there is pyogenic infection elsewhere in the body such as parotitis In very rare instances hepatic abscess has appeared after influenza (Tedenat) As mentioned elsewhere suppuration commonly occurs in actinomycomas of the liver and may supervene in hydatid cysts gummas and tuberculomas In rare instances a single abscess is due to hemic infection by the hepatic artery *or portal vein which usually causes multiple abscesses in 1917 Bruggeman*[11] collected 23 cases secondary to appendicitis Extension of infection from adjacent parts such as suppuration in the gall bladder or perforation of a simple or malignant gastric or duodenal ulcer into the substance of the adherent liver may cause a single but usually comparatively small abscess

Disposing Factors

Although in the main a disease of hot climates its distribution is not uniform in different parts of the tropics thus while frequent in India it is much less common in Ceylon It is very rare in parts of the tropics where the elevation is so high that the mean temperature is that of temperate climates An important factor is sudden variations in the temperature and the commencement of the cold season has been thought to exert some influence but in Cal

cutta Leonard Rogers found that there was no special seasonal incidence Europeans are much more liable to suffer from hepatic abscess than the natives of the tropics, and new arrivals and also those who have been a long time in hot countries are thought to be specially liable to the disease Alcoholism malaria and perhaps Malta fever favor the incidence of abscess the important influence of even a moderate use of alcohol in reducing the resistance of the liver is shown by the increased incidence of the disease in natives who cease to be total abstainers Males are more often affected and this may be correlated with their greater exposure to alcohol, chills, and injury The disease is usually seen in early adult life and is rare in children and the old

Morbid Anatomy

Between 60 and 80 per cent of the abscesses occur in the right lobe, occasionally both lobes are occupied, and from 7 to 17 per cent of the large abscesses are in the left lobe The right lobe is six times the size of the left and is supposed to receive the blood from the intestines, whereas the left lobe is supplied by the blood from the stomach and spleen It has also been thought that amebae work their way across the peritoneum from the hepatic flexure of the colon to the liver, and that the frequency of an abscess in the under and posterior part of the right lobe is thus explained When on the anterior surface an abscess may rupture into the falciform ligament and form a suprahepatic abscess In about 70 per cent of the cases there is a single abscess Two or more large abscesses may be independent, or a small abscess may be secondary or left from a series that have united to form one The abscess may be round oval, or when due to the union of several branching or irregular in shape There is great variation in size, from those containing a few ounces to those holding pints, as much as 16 and 19 pints has been recorded

Externally the liver may show adhesions, especially to the diaphragm In its earliest stage the area of the abscess appears pale and soft, and in the amebic form the liver cells undergo colliquative necrosis and the small cavity contains glairy fluid within shreddy walls which are remarkably free from leukocytic infiltration and thus differ markedly from small abscesses of bacterial origin, for example in pylephlebitis The walls contain entamebae histolyticae and the process is one of hepatolysis due to their toxin Rogers[65] says that 86 per cent of the unopened amebic abscesses are sterile, and that with bacterial infection there is a small celled infiltration In large abscesses the walls are at first rough and necrotic but later become smoother and surrounded by a fibrous capsule which invades the surrounding liver substance The contents of the abscess vary from creamy yellow pus to the more characteristic reddish brown or anchovy paste colored matter due to admixture with broken-down liver substance and blood

Microscopically amebic abscesses contain necrosing liver cells red blood corpuscles and amebae which are more numerous in recent cases but can often when absent in the pus be obtained from scrapings of the walls When bacterial infection has occurred B coli streptococci staphylococci and other organisms can be found Some cases of abscess are primarily due to these organisms or to B pyocyaneus B typhosus pneumococci Friedlander s pneumobacillus (*B mucosus capsulatus*) *and in exceptional instances to micrococcus* melitensis But the contents of abscesses of some duration may be sterile

Inflammation often spreads through the diaphragm to the pleura and so by producing adhesions favors the subsequent rupture of the abscess into the lung

The rest of the liver is usually enlarged and after evacuation of the abscess weighs more than normal this is partly due to compensatory hypertrophy and Rogers[45] insists on its usually healthy state unless bacterial infection supervenes with secondary abscesses cloudy degeneration and other lesions for example in chronic cases amyloid change may follow It is very rare to find an abscess in a cirrhotic liver

Clinical Picture

The clinical picture varies greatly Sometimes the abscess is quite latent *until rupture suddenly occurs Usually the onset is gradual and often indis*tinguishable from acute hepatitis with malaise irregular fever leukocytosis and sometimes a tender palpable liver But there may be an acute onset with a rigor imitating pneumonia of the right lower lobe Of the constitutional symptoms fever is probably the most constant though it may be absent in old standing abscesses with such thick capsules that little or no absorption is possible The temperature is very variable it often imitates that of malaria and may be continuous at first and later swinging from 103 or 104 F at night to subnormal in the morning Rigors are often seen in the course of the disease they may as already mentioned accompany the onset they may be frequent or may not appear until a late stage Night sweats are common and profuse Pain is frequently present but depends much on the site of the abscess which if deeply seated may run its course without any perihepatitis it may be constant pleuritic or brought on by swallowing *In about one sixth of the cases* (Manson[12]) pain is referred to the right shoulder and the acromion particu*larly when the abscess is in the upper part of the right lobe* when the abscess is in the left lobe the pain may be in the left shoulder and in very rare cases *it is bilateral* This referred pain in accord with the observations of Capps would indicate a diaphragmatic pleurisy involving the central part of the diaphragm on the same side as the referred pain (H A C)

There may be a spasmodic dry cough Vomiting is said to be more frequent with an abscess in the left lobe and there may be a sudden onset of symptoms suggesting perforation of a peptic ulcer (Bonnet[7]) Hematemesis and melena are rare and have been regarded as due to hepatic inadequacy and so of very

grave omen (Brau and Noque[7]), but they may be mechanical and due to pressure of the abscess on the portal vein Evidence of hepatic insufficiency by Widal's hemoclasic test, is absent (Françon and Hutinel[76]), but Gordon Covell[7] found that the levulose tolerance test is most useful in determining whether in amebiasis the liver is involved, and, if so, the effect of treatment Appetite is usually poor, flatulence may be troublesome and there may be constipation Pains in the joints and synovitis may occur, as in dysentery Insomnia and mental depression are common Cerebral symptoms due to pyemic abscesses or meningitis are rare

The facial aspect is usually pale and sallow with a muddy and often slightly icteric tint sunken eyes anxious expression, and withal highly suggestive of the condition Wasting and loss of weight are progressive and in proportion to the extent and duration of the disease From the weight of the organ and the presence of adhesions the patient is more comfortable on his back than on either side The skin in the early stages may be dry and hot, and in the later periods clammy Jaundice is seen in about 15 per cent of the cases and is slight in degree The pulse is moderately quickened to about 100 and the blood pressure low There is often leukocytosis with, in bacterial cases a polymorphonuclear increase, whereas in amebic cases the mononuclears are increased Unfortunately leukocytosis may be absent, especially when the abscess has a firm capsule preventing absorption The urine is high colored, and may contain a trace of albumin and albumose Respiration is shallow, mainly thoracic and may be painful

The abdomen is somewhat full and often prominent in the right hypochondrium the abscess may indeed point in this region or in the epigastrium with redness and edema of the skin The liver is enlarged but commonly from the usual position of the abscess in the upper and back part of the right lobe it encroaches more on the thorax, compressing the lung and imitating an effusion at the base of the right pleura, than on the abdomen But the liver may be greatly enlarged downwards and a huge abscess has been known to simulate ascites which, however, is very rare Pulsation may be communicated from the aorta through a liver abscess to the front of the abdomen The hepatic dullness is increased according to the position and size of the abscess Local tenderness is important as a guide both to the existence and position of an abscess Shaking the patient as in trying to elicit Hippocratic succession causes pain Examination by X rays may show immobility of the diaphragm and the upward dome like projection of the abscess Friction due to perihepatitis over an abscess near the surface may be palpable and audible, and is not uncommon over the base of the right lung The upper part of the rectus abdominis muscle may be in a state of defensive rigidity When the abscess is in the left lobe of the liver the apex of the heart may be displaced upwards The spleen is not enlarged in the absence of a special cause Edema of the feet is common in the later stages

The duration of an abscess varies much it may run its course in three weeks become latent, or continue to discharge for a long time the average duration has been estimated at four months Death may be due to septicemia and exhaustion or to some complication, especially rupture of the abscess

Complications

Rupture most often occurs into the lung pleurisy having previously obliterated the intervening part of the pleural cavity Among 329 cases (Thierfelder and Cyr) 133 burst into the lung 57 into the pleura 62 into the peritoneal cavity 45 into the intestines 21 into the stomach 5 into the pericardium and 2 only externally The right lung is most often affected but it is not certain that an abscess in the lung is always due to extension of inflammation through the diaphragm and leakage or rupture of the hepatic abscess for it has been thought that an abscess in the lung may be due to infection of the blood stream and amebae have been found in the small branches of the pulmonary artery The communication between the hepatic and pulmonary abscesses may be small as in a shirt stud abscess and may therefore easily be missed The lung may become much disorganized and cause death from exhaustion or hemoptysis even when the original hepatic abscess has been cured A broncho biliary fistula may occur

Rupture into the pericardium is rare because the left lobe seldom contains an abscess Rupture into the peritoneum may be precipitated by injury and this possibility should always be remembered in connection with the practice *of exploring the liver by a trocar pushed through the abdominal wall* From its fixed position close to the liver the duodenum is the part of the alimentary tract into which a hepatic abscess is likely to di charge Rupture into the thin walled hepatic veins is commoner than into the intrahepatic branches of the portal vein surrounded by the fibrous tissue of Glisson s capsule embolism and secondary abscesses in the lungs are prone to occur Secondary abscesses in the brain are rare In 1912 Legrand [8] collected 43 and in 1919 Armitage [9] who brought the number up to 49 found that in only 10 of the cases were amebae present in the cerebral abscess Thrombosis of the inferior vena cava is a rarely recorded event as is intestinal strangulation by adhesions In cases with long continued discharge amyloid disease may supervene A serious complication is the occurrence of smaller secondary abscesses in the neighborhood but now that emetin is both given by the mouth and injected into the abscess cavities these secondary foci should be prevented

Diagnosis

Diagnosis is often difficult as the characteristic signs and symptoms may be absent Accordingly hepatic abscess should always be suspected in patients

in or from the tropics with progressive deterioration of health and especially with a history of dysentery Fever, pain, enlargement of the liver, and leukocytosis are very strong evidence in such cases, and should at once call for a thorough course of emetin If this fail, operation should be performed

The differential diagnosis must be made from conditions such as malaria, Malta fever malignant endocarditis, lymphadenoma, acute leukemia, syphilitic hepatic fever, typhoid fever, kala azar, trypanosomiasis, hepatitis with fever new growth of the liver and intermittent hepatic fever, and from other forms of intra or extrahepatic suppuration, such as pylephlebitis, suppurative cholangitis subphrenic abscess, peripancreatic abscess, empyema

Blood examinations should rule out the diagnosis of malaria, Malta fever, leukemia typhoid fever kala azar, trypanosomiasis, syphilis, and probably malignant endocarditis From other forms of hepatic suppuration the history of exposure to amebic infection on the one hand and that of previous appendicitis or gallstones on the other will help A suppurating hydatid cyst is except for its causation the same as a single abscess With the diffuse areas of suppuration in pylephlebitis and cholangitis the general condition is worse than in a single abscess Multiple abscesses may follow bacillary dysentery, so a positive agglutination reaction for one of the various forms of dysentery would be in favor of multiple areas of suppuration

Prognosis

The prognosis of single abscess depends on a number of points such as the early or late adoption of efficient treatment, for if this be delayed a large amount of liver substance may be destroyed and the patient's strength much undermined An alcoholic history a broken down constitution and concurrent dysentery also make the outlook gloomy The presence of complications clouds the outlook except that rupture externally is favorable Rupture into the lungs is regarded as a dangerous accident by Godlee [80] and no doubt serious results may follow, but de Castro estimated that 75 per cent and Manson that 50 per cent of the patients recovered The introduction of emetin has certainly improved the outlook in amebic abscess

The prophylaxis of abscess is the treatment of amebic hepatitis with emetin, the avoidance of alcohol in countries where amebic dysentery is endemic, and due care of health

Treatment

The treatment of a large single abscess formerly consisted in free drainage of the abscess emetin being given in addition Comparatively recently it has been urged that if the amebic abscess be not infected with bacteria repeated aspiration with a trocar and the injection of emetin into the cavity is sufficient

in 49 cases thus treated 40 recovered (Thurston [1]) This method has the advantage that it obviates bacterial infection which so commonly supervenes after the free opening of an abscess Thus among 2261 cases treated by open operation the mortality was 57 per cent whereas among 111 cases treated by aspiration and emetin it was 14 4 per cent (Rogers) Treatment by emetin alone even of large abscesses has also been advocated (Hartmann Keppel Hodson [3]) Combined emetin and salvarsan treatment has been recently advocated (Françon and Hutinel) For cerebral abscess Rogers suggests early decompression and subcutaneous injections of emetin

During convalescence the general health should of course be carefully looked after the patient should not return to a tropical country for two years at least and preferably should remain in a temperate climate

Multiple Liver Abscesses

Pylephlebitis and suppurative cholangitis are described elsewhere and the condition of multiple abscesses due to infective embolism of the intrahepatic branches of the portal vein without suppuration of the trunk of the vein is otherwise much the same as that of suppurative pylephlebitis this may occur in bacillary and as mentioned above in severe amebic dysentery and be secondary to appendicitis Multiple small abscesses may be due to infection carried by the blood stream especially in pyemia secondary to acute osteomyelitis and ear disease they are rare in malignant endocarditis Out of ten cases of systemic blastomycosis there were small suppurating foci in the liver in four (Montgomery and Ormsby [84]) Cases with multiple pyemic hepatic abscesses do not show symptoms pointing to the liver Rogers [85] has reported cure of multiple amebic abscesses by emetin

Acute Perihepatitis

Acute perihepatitis or acute inflammation of the capsule of the liver necessarily occurs in generalized peritonitis and in local peritonitis in its neighborhood such as a subphrenic pyopneumothorax Acute inflammation may also spread through the diaphragm from acute pleurisy or pericarditis Fractured ribs or blows over the liver may also cause acute inflammation of the capsule In hot climates acute perihepatitis is often seen but is probably secondary to hepatitis It is common over abscesses single or multiple nodules of new growth and sometimes over nutmeg livers in which a passing or terminal infection has occurred in these cases and indeed generally acute inflammation of the capsule of the liver is more often partial or strictly local than universal

Clinically there is pain on pressure and on respiration resembling that of pleurisy A friction rub can be heard over the organ and the abdominal mus

cles are rigid Cantlie[85] describes pain running up to an area between the clavicle and the acromion process on the front of the chest as a result of grasping the liver between the two hands, one in front and the other behind, and moving it to and fro There may be dry cough, hiccup, nausea and vomiting and symptoms due to the underlying cause which should always be investigated It is naturally very likely to be regarded as acute pleurisy and Cantlie's test may be of use in eliminating perihepatitis but the two conditions often coexist In some instances ascites may be present

Treatment consists in rest in bed local applications such as leeches, dry cupping poultices and fomentations or strapping for the pain, low diet, and the treatment of the underlying condition, for example, emetin for amebic hepatitis

Chronic Perihepatitis

Chronic perihepatitis has two forms (a) local, (b) universal *Local chronic perihepatitis* is often due to friction thus it is seen on tight laced and nutmeg livers over a hydatid cyst gummas and nodules of new growth It may be due to the irritation of a calculous gall bladder or be associated with tuberculous or neoplastic peritonitis The local thickenings of the capsule resemble the milk spots on the pericardium and are often associated with, though hardly ever so advanced as, local chronic perisplenitis

It is doubtful if pain is ever due to this condition but if so, the treatment then would be on the same lines as in acute perihepatitis

Universal Chronic Perihepatitis

Synonyms —Diffuse chronic hyperplastic perihepatitis, sugar iced liver This condition is practically always part of diffuse chronic peritonitis and the names mentioned above lay too much stress on the localization of the process of the liver It may spread from the peritoneum to the capsule of the liver or vice versa, but it is not confined to the peritoneum covering that organ

Pathogeny

The chronic peritonitis is spoken of as simple because it is not manifestly due to tuberculosis or new growth There is widespread fibrosis with contraction so that the omentum mesentery and intestines are shortened and the liver and spleen enclosed in a hard and contracting casing In considering the causation of this chronic peritonitis and perihepatitis it is convenient to divide the cases into three groups which however are not water tight compartments (1) when associated with a varying degree of a similar change in the pleurae and pericardium this has been called multiple serositis multiple progressive hya

loserositis polyorrhomenitis, or Concato s disease There may be well marked indurative mediastino pericarditis a calcified or an adherent pericardium in addition to pleuritic adhesions The morbid change radiates from the dia phragm the constant movements of which are probably concerned in keeping up the inflammatory process so that the condition may be thought to date from an acute attack involving the liver pericardium or pleurae It seems to be agreed that the inflammation usually starts in the abdomen and spreads up to the chest but in some cases the process is reversed The kidneys are usually healthy or at mo t show chronic venous engorgement Some observers include here the cases described as pericarditic pseudocirrhosis by Pick but it should be borne in mind that this observer regarded any perihepatitis as accidental and not as an essential change

(2) When associated with arteriosclerosis and arteriosclerotic changes in the kidneys and without the intimate association with multiple serositis char acteristic of the first group Mixed cases of these two groups however cer tainly occur It seems probable that the presence of arteriosclerosis and chronic renal disease which as Flexner showed reduce the bacterial resistance favors chronic infection of the peritoneum possibly of intestinal origin Nineteen out of Hale White s[86] twenty two cases belong to this category

(3) When associated with other conditions It is probable that syphilis produces chronic peritonitis and the frequency of a positive Wassermann re action in chronic ascites is an argument in favor of this view In some cases hepatic gummas are associated with the chronic peritonitis and perihepatitis and Letulle[87] insists on the association of syphilitic peritonitis with ordinary portal cirrhosis It must be pointed out however that portal cirrhosis is usually agreed to be exceptional in this form of chronic perihepatitis In other instances the associated condition is that called cirrhosis of the stomach or plastic limits but really carcinoma Alcoholism and injury have been suggested as causes Nicholls[88] recorded a case with a chronic duodenal ulcer

The nature of the infection is unknown B coli and other organisms have been suggested The existence of the special form of hyperplastic tuberculosis of the intestine naturally suggests that the B tuberculosis may when attenu ated produce a similar hyperplastic peritonitis and perihepatitis

The sexes are about equally affected and the patients are usually between forty and fifty years of age but the disease may occur in childhood

Morbid Anatomy

The liver is covered over by a layer of white fibrous tissues of cartilaginous firmness resembling the icing of confectioners hence the name sugar iced liver (Zuckergussleber) There are usually pittings or fenestrations on the surface of this carapace which can be peeled off leaving a fairly healthy peritoneal sur face The liver i thus both compressed and deformed especially at its anterior

margin, which may be bent over so as to touch the convexity In uncomplicated cases the gall bladder is collapsed and so bridged over that it is more or less hidden from view but neither the bile ducts nor the portal vein are constricted Microscopically the icing is composed of horizontal laminae of hyaline fibrous tissues without blood vessels but containing a few nuclei, and in the deeper layers collections of leukocytes and mast cells The liver is usually rather smaller than normal, soft fatty, and often shows some venous engorgement Cirrhosis is extremely rare The liver cells are atrophied, fatty, and pigmented

The spleen shares in the hyaline serositis and is often adherent to the diaphragm and abdominal wall The kidneys may show little change apart from chronic venous engorgement, or may be the site of advanced arteriosclerotic change

Clinical Picture

The main feature is persistently recurring ascites which usually comes on gradually, but in some instances, as in six out of Nicholls's fourteen cases, is acute For a long time the general health and strength are maintained, but eventually emaciation and death from cardiac failure or intercurrent infection occur The ascites accumulates after tapping and gradually the intervals become shorter Osler refers to the case of a child who was tapped 121 time and in Rumpf's case this was necessary on 301 occasions The fluid is clear but has a specific gravity of about 1 015, contains three per cent of albumin and so is allied to the inflammatory rather than to the passive effusions The edge of the liver may be felt as a hard border but is often obscured by ascites, and care must be taken not to confuse a rolled up omentum with the liver The portal anastomosis around the umbilicus is not obvious, but the caval system of veins over the abdomen is opened up and in the late stages the feet become edematous Jaundice and gastrointestinal hemorrhages do not occur in uncomplicated cases As the hepatic cells are fairly well preserved the symptoms of hepatic toxemia, such as drowsiness and widespread hemorrhages so common in cirrhosis, are not likely to arise The disease lasts from two to sixteen years

Diagnosis

Diagnosis depends on the presence of long continued ascites not explained by the presence of obstructive heart or lung disease or nephritis

From hepatic cirrhosis the chronic character of the ascites requiring numerous tappings is an important feature in addition, the absence of toxemic symptoms is significant In cardiac disease the recognition of heart disease and the good effect of digitalis are valuable guides In intra abdominal neoplasms and tuberculosis tumors may be felt after tapping, and cytological examination of the fluid may give a clue In the recurrent ascites due to ovarian papilloma a

fragment of the growth will establish the diagnosis It is open to question whether or not many of the cases are not due to syphilitic peritonitis which however when far advanced is less likely to respond to treatment than hepatic syphilis in which the liver is enlarged and jaundice may occur The Wassermann reaction should be tested in the ascitic fluid as well as in the blood serum *sometimes it is found positive in ascitic fluid while negative in the blood serum* the same relationship as occurs quite frequently in the spinal fluid in tabes and other syphilitic lesions of the central nervous system (H A C)

Prognosis and Treatment

The prognosis as regards life is bad and is said to be worst in the pericarditic cases but life may be prolonged for many years Kelly [89] found that seventy per cent of the patients lived more than two years and fifty per cent more than four years

Arshpenamin and iodides should always be given particularly when the Wassermann reaction is positive Otherwise the measures are palliative diuretics such as caffein theocin sodium acetate or diuretin (theobromin sodium salicylate) in combination with digitalis the diuretic pill composed of 1 grain (0 06 gm) each of blue pill digitalis leaves and squills copaiba resin grains 5 (0 33 gm) in a cachet highly recommended by Hale White and apocynum may be given a trial Of the newer diuretics novasurol recently has been commended for use in the treatment of the ascites of cirrhosis of the liver and may be tried here It is given intramuscularly first in a dose of 0 5 cc to see if no bad reaction is produced if none follows 2 cc is given (H A C) Paracentesis must be performed when necessary Neither on theoretical nor practical considerations can the Talma Morison operation be recommended but permanent drainage into the subcutaneous tissues seems more promising

CIRRHOSIS OF THE LIVER

Cirrhosis of the liver has been classified in various ways according to the etiology anatomical changes, or clinical features but from a practical standpoint a short classification is preferable and accordingly the following forms will be described

Portal multilobular or common cirrhosis
Special forms pigmented cirrhosis cirrhosis in children
Biliary cirrhosis (1) hypertrophic Hanot s disease (2) obstructive

called to the presence of leprosy bacilli (Carrieu and Anglada[103]), leishmania (Nattan Larrier[104]), and the ova of bilharzia in cirrhotic livers

Focal necrosis of the liver cells as observed in typhoid fever and other diseases and foci of small celled infiltration as seen in scarlet fever, smallpox and streptococcic infection are probably recoverable from without causing further changes in the liver unless some additional toxic influence is brought to bear on the liver Experimentally coal tar absorbed from the skin or injected subcutaneously produces acute necrosis of the liver cells and chronic changes resembling those of cirrhosis (J Davidson[104a]), these poisons being conveyed by the blood stream, as in some of the infections just mentioned In the great majority of cases the poisons reach the liver by the portal vein and come from the alimentary canal In a few instances poisons, and possibly microorganisms from the spleen reach the liver by the splenic vein, for example in splenic anemia in which hepatic cirrhosis follows and constitutes Banti s disease, in the hepatic cirrhosis following the Egyptian splenomegaly (Richards and Day[105]), and in the Gaucher or familial form of large celled splenomegaly (Mandlebaum[106]) Weber[107] suggests that there is a previously undescribed disease of unknown origin, ' idiopathic non alcoholic progressive cirrhosis ", in which the liver is usually most affected but in which splenomegaly may precede any obvious hepatic lesion and that this " splenic " form is probably identical with Banti s disease

Lastly some rather debatable points must be noticed In the past syphilis has not been considered a direct cause of portal cirrhosis, the lesions recognized as due to the spirocheta pallida being quite distinct The most that has been suggested is that after the cure of the early lesions the liver is left with its resistance so diminished that factors, which in ordinary circumstances would have been comparatively harmless, are now able to exert a sclerogenic effect The frequency however, with which a positive Wassermann reaction is obtained in cases of portal cirrhosis (Symmers[108], Letulle[109]) raises the question of a more intimate relation between syphilis and portal cirrhosis, and Letulle believes that ordinary cirrhosis may be due to syphilis

In the second place the problem of the causal effect of tuberculosis should be mentioned here, this is discussed under the heading of tuberculosis and its importance shown to be slight One of the editors (H A C) has obtained a positive guinea pig test for tuberculosis from the sediment from the ascitic fluid in the usual type of portal cirrhosis Post mortem examination of one of these patients revealed no lesion of the liver or peritoneum suggestive of tuberculosis and no old tuberculous lesion was found in the lymph nodes of the mesentery The relation of the tubercle bacilli to the cirrhosis in such cases is not clear, but it is unlikely that they have any causal relationship

Another theoretical consideration is that whenever liver cells undergo destruction, for example, in the focal necrosis of hemic infections or intoxications hepatic cytolysins result from absorption of their proteins and further destruc

tion of the liver cells should result and a vicious circle be established (Fiessinger[110]) In this connection it is interesting to note that after inducing repeated anaphylactic shock Longcope[111] found that the livers of the experimental animals were cirrhotic as the result of chronic inflammatory changes around necrotic foci

Morbid Anatomy of Portal Cirrhosis

The size and weight of the liver in portal cirrhosis vary within wide limits The organ may weigh as little as 30 oz (900 gms), and it is to such instances that the term atrophic is applicable but other livers with similar microscopical changes may weigh as much as 200 oz (6 kilos) The size and weight of the liver may be increased by fatty change by active hyperemia and by rapid progress of the change during the early stages or by compensatory hyperplasia at a later period It is therefore not true in all instances that the liver is first large and later becomes small from cicatricial contraction In patients dying from the effects of cirrhosis the liver is larger in young subjects than in their elders The livers of persons dying from the effects of the disease usually weigh less than in those with latent namely compensated cirrhosis dying from independent causes Both in patients dying from the effects of cirrhosis and in those with latent cirrhosis the weight of the organ diminishes with the advance of years

The peritoneal surface is opaque either from chronic peritonitis or subcapsular fibrosis, this thickening being more distinct between the projecting hobnails and there may be adhesions of varying density and vascularity The hobnails vary in size from that of a pea to that of a pigeon s egg when large they may resemble multiple new growths except that they are never umbilicated and this condition is sometimes spoken of as nodular cirrhosis or cirrhosis with multiple adenoma On section the nodules are tawny brown or yellow in color but may be white or caseous looking from fatty change Usually the liver is uniformly altered but sometimes the left lobe is more affected one of the small lobes the Spigelian or caudate may be much enlarged The substance of the liver is tough divided into irregular areas by grayish fibrous tissue which is somewhat depressed below the surface of the rest of the liver tissue The liver is often pale or yellowish from fatty change or bile staining It is from this yellow color (κιρρος) that the name cirrhosis is derived In rare instances there are hemorrhages into the liver substance and occasionally the terminal branches of the portal vein are thrombosed.

Microscopically the fibrosis spreads out from the portal canals and encloses a varying number often six to ten of lobules (hence multilobular) According to its age the interstitial fibrosis varies from round-celled infiltration to well formed and dense tissue containing elastic tissue derived from the walls of the vessels The interstitial frame work of the liver including Kupffer s cells undergoes hyperplasia When the process is advancing rapidly the lobules are

invaded and a mixed form of cirrhosis results The remains of part of a lobule may be surrounded by fibrous tissue The interstitial tissue contains numerous well formed vessels derived from the hepatic artery, but sometimes the vessels running between the portal and the intralobular veins show endophlebitis which interferes with compensatory hyperplasia of the liver cells, so that the liver is small The lymphatic vessels may also be obliterated

In active cirrhosis the interstitial tissue shows the prominent structures known as pseudo bile canaliculi, they are composed of double columns of small or cubical cells staining deeply, with a potential lumen They twist and form a network and often end close to a liver cell Their origin and nature have been much debated

The liver cells may show degenerative changes of a hyaline nature at an early period and fatty changes are extremely common These changes are especially prominent in cases running a rapid course The cells may be pigmented by bile or hemosiderin, and in the early stages contain glycogen which helps to explain the absence of glycosuria The normal trabecular arrangement of the lobules is disturbed in a puzzling fashion, partly as a result of compensatory hyperplasia of the liver cells at the periphery of the lobules where the blood supply is most favorable The cells increase in size and divide by direct or even by indirect division, and may form definite adenomas which account for the hobnail' or multiple adenomas of nodular cirrhosis

The hepatic artery is generally enlarged The hepatic veins in rare instances show obliterating endophlebitis (Hess) The portal vein is usually thickened and dilated from increased blood pressure, and may undergo secondary calcification The intrahepatic branches are compressed and occasionally thrombosed while its radicles at the other periphery are dilated The trunk of the portal vein is in rare instances thrombosed The collateral anastomoses between the portal and the systemic circulations may be much exaggerated and may conveniently be described as (1) general, between the veins of the peritoneum duodenum, and colon where they are uncovered by peritoneum and the retroperitoneal veins which open into the lumbar and azygos veins this subperitoneal plexus of Retzius may be extraordinarily well developed (2) Local, (a) in connection with the liver, an internal portocaval anastomosis between the branches of the portal vein and the interlobular branches of the hepatic veins between the veins of the liver and those of the diaphragm where the liver is uncovered by peritoneum a large accessory portal or parumbilical vein (of Sappey) may run in the falciform ligament and put the portal vein into communication with the veins of the abdominal wall, the dilated veins may appear around the umbilicus but are hardly ever comparable to the caput Medusae seen in obstruction of the inferior vena cava (b) At the terminations of the intra abdominal alimentary canal the coronary vein of the stomach anastomoses with the esophageal veins opening into the azygos and the dilated veins and varicosities under the mucous membrane, so-called

esophageal piles may be prominent features in the long axis of the esophagus The superior hemorrhoidal opening into the inferior mesenteric vein and so into the portal vein anastomoses with the middle and inferior hemorrhoidals which drain into the internal iliac vein

These anastomoses serve as a compensatory mechanism and carry on the circulation which is obstructed by the hepatic changes but in addition to its good effects in relieving portal engorgement this short circuiting has bad effects If carried to its ultimate conclusion the blood is no longer detoxicated by passing through the liver and as in Eck s experimental fistula or the union of the portal vein with the inferior vena cava toxemia results In the second place the dilated anastomoses may become ulcerated rupture of an esophageal pile is the most frequent and important cause of hematemesis hemorrhage has been known to occur into the sheath of the rectus abdominis muscle from the accessory portal veins in the falciform ligament

The gall bladder does not show any constant change subserous edema may accompany ascites and cholecystitis is occasionally present gall stones are more frequent than in ordinary routine post mortem work

The spleen is enlarged in about eighty per cent of the cases from the combined effects of toxemia and backward pressure in latent cases it weighs less than in cases proving fatal from the effects of the disease There may be perisplenic adhesions or local areas of chronic capsulitis There may be endophlebitis of the splenic vein Histologically there is peri arterial fibrosis with proliferation of the reticular tissue of the splenic pulp

The pancreas is usually enlarged from chronic interstitial fibrosis of the adult type spreading out from the blood vessels and though inter and intra acinous not affecting the islands of Langerhans

In the esophagus the mucosa may be thickened either diffusely or localized as corns and may become adherent to the dilated veins in its lower three or four inches (7 5 or 10 cm) and undergo ulceration The stomach commonly shows chronic gastritis and occasionally varicose veins gastric and duodenal ulcers are rare Chronic enteritis with shortening of the bowel which is associated with chronic peritonitis is common so that the small intestine may measure fifteen (4 6 meters) instead of twenty five feet (7 6 meters) feet in length The intestinal veins and especially those of the rectum may be dilated The peritoneum often show some degree of chronic peritonitis which may be syphilitic in origin (Letulle[109]), in from ten to twenty per cent but a high degree of hyaloserositis is rare

The kidneys are enlarged in about half the cases not uncommonly from excessive drinking Arteriosclerotic atrophy is present in about 25 per cent and tubal change in 5 per cent Infarcts of the pyramids with lime salts were found in 44 out of 48 cases specially examined by Goldschmidt [2]

Arteriosclerosis naturally from the age of the patients is not infrequently present The heart is often flabby and dilated and shows degeneration cloudy

or fatty, in about thirty per cent of the cases Malignant endocarditis is a rare complication

The thyroid has been found to show fibrosis, epithelial hyperplasia, and colloid absorption, as in Graves's disease (Farrant[113]) In cases of long continued ascites the diaphragm may show compensatory hypertrophy Apart from tuberculosis the lungs do not present any characteristic change, but from ascitic displacement of the diaphragm the lower lobes may be collapsed Right sided pleurisy is seen in ten per cent of the cases Tuberculosis is an important complication it is met with more often in the bodies of persons with cirrhosis than in those dying from other non tuberculous diseases This may be due to the lowered resistance and in this respect alcoholism probably plays a part Pulmonary tuberculosis accounts for death in about 13 per cent of all persons found to have a cirrhotic liver The peritoneum is the next most important site among 584 cases of cirrhosis it was present in 55 or 8 per cent, as compared with 22 6 per cent incidence of pulmonary tuberculosis Reference has been made already to the presence of tubercle bacilli in the ascitic fluid without evidence of a tuberculous peritonitis

Clinical Features of Portal Cirrhosis

The disease may be entirely latent and discovered only after death from other causes such as accident The course of cirrhosis may be divided into (1) the early or preascitic stage, often interrupted by the brusque onset of gastrointestinal hemorrhage, and (2) the ascitic stage The early stage begins gradually and often presents symptoms due to alcoholism and hepatic congestion such as want of appetite, dyspepsia, nausea and neurasthenia The liver may vary in size and be tender Enlargement of the spleen is likely to precede gastrointestinal hemorrhage Some months or even years may elapse before hematemesis supervenes and there may be a similar interval before ascites follows or from reformed conditions of life the disease may become latent

The face may show rosacea especially over the "flush area", due to dyspepsia or be sallow dirty and pigmented or clear Small angiomas probably due to toxemia and sometimes appearing in crops when the disease is advancing are common on the skin generally and when on mucous surfaces may account for epistaxis and for false hemoptysis and hematemesis The skin is often dry and wanting in elasticity and may show petechiae The conjunctivae are muddy and often slightly bile stained and some degree of exophthalmos is not unusual The lips are apt to become fissured the tongue flabby furred or dry the gums spongy and in the later stages prone to bleed and the breath is offensive The pulse is slightly quickened, the blood pressure both arterial and venous (Villaret and Saint Girons[114]) usually is low, and there may be a systolic mitral murmur from muscular incompetence The disease is commonly afebrile, though, especially in rapidly progressing cases there may be a low

form of fever, but patients with cirrhosis offer a poor resistance to infection, especially to tuberculosis, and fever may be caused by these complications.

As the portal obstruction increases, dyspepsia of a flatulent type is aggravated; usually there is a deficiency of hydrochloric acid in the gastric juice or complete achlorhydria as a result of gastritis. Absorption is interfered with, wasting is progressive, and muscular weakness increases. Constipation is the rule, but occasionally from enteritis diarrhea supervenes, especially towards the end. Acute tympanites, probably toxic, sometimes occurs.

The basal metabolism is within normal limits (Aub and Means[114]). When the disease is established there is a secondary anemia. Occasionally a grave anemia without any obvious cause is the chief and fatal symptom. Leukocytosis appears only in the presence of complications, but in Calcutta Leonard Rogers found it frequently and regarded a high count as ominous. The cholesterol content of the blood is below the normal. Van den Bergh's[8] test may show an increase of the bilirubin in the blood serum, though not enough to appear in the urine or to tinge the skin, the reaction being a prompt direct one (latent obstructive jaundice). Hyperglycemia is commonly present, and is associated by Chauffard, Bordin and Zizine[115] with a well developed collateral circulation. Among 154 cases of cirrhosis the Wassermann reaction was positive in 48 per cent (Letulle[116]).

The urine is usually diminished in amount as a result of the low blood pressure, the diminished absorption from the alimentary canal, and from the presence of ascites. It is highly colored, deposits urates, and contains an excess of urobilinogen, and may show the presence of bile salts although there is no jaundice. Albuminuria is rare, but may occur in the late stages from the combined effects of cardiac failure and toxemia, or very largely from the pressure of a large spleen on the left renal vein, the albuminuria then occurring only when the patient is lying on his back or left side. Glycosuria is rare; it occasionally appears after alcoholic excess, but in cases of active cirrhosis, though not in compensated cases, the levulose blood content may prove of value as showing evidence of hepatic insufficiency. Acidosis may occur, and as a result the urea diminishes and the ammonia in the urine increases. In the presence of ascites the chlorides are diminished.

Edema of the feet is usually a late phenomenon and may be due to the pressure exerted on the inferior vena cava by ascites, or come on before ascites and be toxic, or be due to cardiac weakness or to peripheral neuritis. Clubbing of the fingers, such as is seen in Hanot's cirrhosis, is extremely rare.

Jaundice is not a striking feature and is usually transient when it occurs, as it does in about a third of all the cases. It may be catarrhal and an extension from duodenitis, it may be hemolytic or terminal, but it is most often seen in cases running an acute course with degenerative changes in the hepatic cells and a large liver — the mixed cases which show a transition to Hanot's cirrhosis — and according to Brule[117] the jaundice is not obstructive but due to changes

in the liver cells In rare instances it is due to widespread acute degenerative changes in the liver cells (icterus gravis), and may be associated with the onset of ascites (Fiessinger and Brodin's [11] acute ictero ascitic syndrome) or it may be due to an independent cause such as a calculus in the common duct Quite commonly it is so slight that bile pigment does not appear in the urine (acholuric jaundice) though it is present in the blood

The liver is more often enlarged than diminished in size, but it may vary rapidly in its apparent dimensions from congestion, flatulence of the intestines, and displacement from ascites The estimation of the size of the liver by percussion is thus subject to fallacies Its surface is firm, more or less irregular and often tender The often quoted sequence of enlargement in the early stage followed by later contraction is subject to many exceptions Hepatic enlargement is stated to be more frequent in males than in females (Chauffard and Brodin [118]) There may be discomfort or dragging and pain from transient perihepatitis In rare instances a venous murmur can be heard accompanied by a palpable thrill over the hepatic, epigastric, or umbilical region, it may come and go with altering degrees of abdominal distention and is most easily explained as produced in the dilated venous anastomoses

The spleen is almost constantly enlarged in active cirrhosis and is an index of the severity of the disease it may diminish considerably after gastro intestinal hemorrhage rapid recurrence of ascites, or diarrhea The enlargement may be obscured by ascites or flatulence, and percussion is not a reliable method of determining its size The organ is fairly firm and there may be pain from perisplenitis or discomfort from adhesions As in other forms of splenomegaly a venous hum and thrill may be due to kinking of the splenic vein

Hematemesis may be the first indication of illness and be quite sudden, or be preceded by symptoms of gastritis, but it may supervene late after the onset of ascites It occurs in rather more than a quarter of all the cases, among 259 cases it was noted in 72 or 28 per cent It is more frequent in patients dying from the disease than in latent cases and about one fifth of the patients having hematemesis die from that cause Its percentage incidence in men is three times that in women The quantity of blood vomited up is always considerable and in addition some is passed by the bowel The blood is dark and clotted, and usually there is a single hematemesis The patient is often collapsed and is left anemic for some time, and occasionally delirium tremens is thus precipitated Hematemesis is usually due to rupture of an esophageal varix but it may be due to accompanying conditions as acute gastritis minute erosions of the gastric mucosa, gastric or duodenal ulcers, varicose veins in the stomach, and sometimes to blood swallowed from the pharynx The diagnosis must be made from other causes of hematemesis, mainly by the history it may be mentioned that hematemesis occurs rather more frequently in cirrhosis (26 per cent) than in peptic gastric and duodenal ulcer (20 per cent , Cabot [119]), from chronic splenic anemia by the much larger spleen,

from gastric carcinoma by the usual coffee ground vomit and by the presence of a tumor

Hemorrhage from the bowel is usually melena and an accompaniment of hematemesis, but when the quantity of blood poured out into the stomach is small there may be melena only Occult blood in the feces detected by the benzidin test is said to be common in the ascitic stage In rare instances bleeding occurs from the colon or rectum Piles are curiously infrequent Hemorrhage may also take place from the larynx the lungs in tuberculosis the uterus and in rare instances from the kidneys

Ascites occurs in about 50 per cent of all the cases and in the vast majority (85 per cent) of those proving fatal from the effects of the disease whereas it is seen in less than twenty per cent of patients with cirrhotic livers but dying from other causes The causes of ascites in portal cirrhosis will be considered under the following heads

1 (a) The increased resistance to the passage of portal blood through the cirrhotic liver is probably due not as might naturally be thought to the compression of the intrahepatic branches of the portal vein by fibrous tissue but to a more direct communication of the arterial pressure through the dilated capillaries to the portal blood (F C Herrick [120]) The passive engorgement thus induced is favorable to the effusion of fluid but this alone does not account for ascites, which is usually absent at a time when from the occurrence of gastrointestinal hemorrhage the pressure in the portal vein is highest further if increased venous pressure alone were the responsible factor the ascites should develop pari passu with fibrosis (b) It has been suggested that the additional factor is thrombosis in the small interlobular branches of the portal vein but this is seldom seen in microscopic sections of the cirrhotic liver (c) Thrombosis of the trunk of the portal vein undoubtedly causes rapid ascites but is so rare that it is an exceptional factor only In favor of the mechanical origin of the ascites of cirrhosis is the predominance of endothelial cells in the fluid

2 Chronic peritonitis and perihepatitis may be present in cases of persistent ascites in cirrhosis and then may be regarded as the cause but they are not present in all cases The cause of the chronic peritonitis varies there is often tuberculous infection and some authorities have gone so far as to consider that ascites is always of this nature (Roque and Cordier [1 1]) Recently chronic syphilitic peritonitis has been described by Letulle who obtained a positive Wassermann reaction in 74 out of 154 cases of cirrhosis and the syphilitic origin both of cirrhosis and of ascites has come to the fore The occasional predominance of lymphocytes in the ascitic fluid is compatible with the view that the effusion is tuberculous in some and syphilitic in others Chronic peritonitis due to a low but undetermined form of infection which may extend from the liver the intestines or the thoracic cavity may also account for some cases

3 Acute toxemia The sudden onset of ascites sometimes after some acute infection and the observation that edema of the feet may precede the appear

ance of ascites, has suggested that toxins may either so damage the vessel walls as to allow transudation to take place, or act as lymphagogues The toxic factor would obviously work at an advantage when there is portal stasis with increased venous pressure

4 Cardiac failure Dilatation of the heart is the most frequent cause of ascites in general and is not uncommon in cirrhosis, the increased venous pressure thus produced would act both mechanically and by altering the nutrition of the endothelium, and so favor transudation of fluid

In conclusion ascites in patients with cirrhosis may be due to various factors and combinations of these factors concomitant chronic peritonitis is important, but the combination of mechanical portal stasis with toxemia affords the most satisfactory explanation

The onset of ascites may follow exposure, a blow, or infection, and may appear suddenly though the onset may be masked by tympanitis The abdominal distention, if accompanied by vomiting and constipation, may suggest sub acute intestinal obstruction Rapid collection of ascitic fluid is compatible with the onset of portal thrombosis The abdominal distention is at first mainly anteroposterior with shifting dullness in the flanks which gradually bulge A latent hernia may be forced out by the increased intra abdominal pressure, and the umbilicus eventually everted The skin becomes tightly stretched and from rupture of the deeper layer lineae distensae, at first red and subsequently becoming white cicatrices, appear The caval system of veins, the epigastric anastomosing with the long thoracic and internal mammary which become prominent from pressure on the inferior vena cava, should be distinguished from the porto systemic veins around the umbilicus by their relative positions and by their diminution in size or disappearance after the ascitic effusion is tapped The liver usually may be felt by dipping and displacement of the fluid The diaphragm is pushed up and the bases of the lungs may become collapsed or edematous The effects of ascites are mechanical, namely pain from distention dyspnea palpitation dyspepsia, constipation and diminution in the quantity of urine The onset of ascites is a late and serious event, when due to cirrhosis uncomplicated by chronic peritonitis, a condition which can hardly be diagnosed with certainty during life tapping is seldom required more than twice before death from toxemia closes the scene

The quantity of ascitic fluid varies, it may amount to 20 liters, and in such cases the abdomen may measure 50 inches (1 25 meters) in circumference More may be present and the abdomen be enormous, Sears[122] recently has reported a case in which 7- quarts approximately 72 liters, were removed with subsequent removal of 70 quarts of ascitic fluid on two occasions The fluid is yellowish or green, with a specific gravity of 1 008–1 015 the higher figure being found in fluid slightly turbid from some degree of peritonitis set up by previous tappings The predominating cells are usually endothelial cells as in a passive transudation, but there may be a mixture of endothelial cells and

lymphocytes or a predominance of lymphocytes thus suggesting tuberculous or syphilitic infection, a high lymphocytic count however may be seen in cases without any tuberculous change in the abdomen after death When there is any superadded inflammation with turbidity of the fluid polymorphonuclears appear In rare instances the fluid is chylous chyliform, or *hemorrhagic*

After tapping which should not be delayed in the presence of discomfort and a considerable effusion the fluid collects fairly rapidly, according to Cabot at the rate of a pint (500 cc) a day The difficult point in diagnosis is to decide between ascites due solely to cirrhosis and that caused by associated chronic peritonitis In the latter event many tappings may be required and when there is reason to consider that it is syphilitic particularly with a stronger Wassermann reaction in the fluid than in the blood cure may follow appropriate treatment In ascites due to uncomplicated cirrhosis the patient is usually more emaciated and toxemic than in cases complicated with chronic peritonitis Examination of the fluid may help in the recognition of other causes for ascites such as tuberculosis malignant disease ovarian papilloma Cardiac failure is responsible for more cases of ascites than any other factor and as a systolic murmur may be present in cirrhosis and as a large tender liver accompanies cardiac failure difficulty may arise especially when an alcoholic heart complicates cirrhosis

Nervous symptoms of various kinds are due to toxemia In the early stages headache depression tremor loss of memory and mental power may be partly due to alcoholism Pruritus in the absence of jaundice is rare In the late stages drowsiness coma delirium either alcoholic or maniacal and less often convulsions and paralyses occur and show the general resemblance between hepatic toxemia and uremia In rare instances hemiplegia without any gross lesion supervenes The slighter degrees of peripheral neuritis due to a combination in varying degrees of hepatic insufficiency and alcoholism may be easily overlooked but well marked cases with Korsakoff s syndrome are exceptional it is said that it is characterized by rapid extension to the upper limbs and incontinence of the sphincters The occurrence of lenticular degeneration in children is referred to elsewhere but it is interesting to note that bilateral hemorrhages into the lenticular nucleus have been recorded in an adult (Henrici [1 3])

Complications of Portal Cirrhosis

It is not always easy to draw a clinical distinction between some of the less frequent symptoms and what might rightly be regarded as complications Patients with cirrhosis are extremely prone to infection especially by bacillus tuberculosis the lungs and the peritoneum being the most frequent sites As already mentioned pulmonary tuberculosis is the cause of death in about thirteen per cent of persons with cirrhosis but in these cases the hepatic disease is usually latent The abdominal effusion due to this cause imitates the ascites

of cirrhosis, but there may be fever, and abdominal pain is more prominent. Generalized tuberculosis may occur and be accompanied by jaundice and considerable fever. Tuberculous pleurisy, particularly on the right side, is not uncommon and the exudate may be hemorrhagic, but the pleurisy associated with cirrhosis is not necessarily tuberculous or right sided. Upward displacement of the liver by ascites may simulate a right sided pleural effusion. Acute infections such as pneumonia, erysipelas, malignant endocarditis, pericarditis and particularly pneumococcic and streptococcic peritonitis may supervene. Pernicious anemia is a rare complication, but is disposed to by the frequency of achlorhydria. Primary carcinoma of the liver occurred in 3.5 per cent of 198 cases of cirrhosis or ten times more frequently than in other conditions (Blumenau[1, 4])

Prognosis in Portal Cirrhosis

The duration of the disease shows wide variations: some cases run an acute course, others become latent, and generally two or more years intervene between the recognition of the disease and death. Sudden and fatal hematemesis may occur in cases of compensated cirrhosis in which there have been few or no symptoms. Cabot says that sudden death from toxic coma may occur in apparent perfect health. With the onset of ascites death from toxemia and coma is prone to follow, and in cases uncomplicated by chronic peritonitis this often happens within two or three months of the first tapping. But in cases complicated with chronic peritonitis the number of tappings may be considerable and the duration much prolonged, or the disease may become latent. Death may be precipitated by complications, such as pneumonia or erysipelas, or occur suddenly from fatty degeneration of the heart.

Cirrhosis, unlike universal chronic peritonitis, is often found after death in persons who have not apparently manifested symptoms and have died from some independent cause, such as injury. In 167 consecutive cases at St George's Hospital in which the liver was cirrhotic at necropsy, 86, or 50.2 per cent, proved fatal from other causes, though tuberculosis, the incidence of which is favored by cirrhosis, was the responsible cause of death in probably a quarter of these cases. Cirrhosis therefore often becomes latent as the result of the two compensatory processes: (1) the anastomosis between the radicles of the portal and general systemic veins, and (2) hyperplasia of the liver cells, which respectively obviate mechanical portal engorgement and toxemia. These compensatory processes may also have bad effects, the dilated veins may, as already mentioned, rupture and the hyperplastic liver cells may either undergo degeneration and become invaded by cirrhosis or give rise to primary carcinoma.

The prognosis is generally speaking far from cheerful, though not so bad as in Hanot's cirrhosis, even in latent cases copious hematemesis may occur; but on the other hand early hematemesis by making the patient alter his manner

of life may be followed by permanent latency Improvement after antisyphilitic treatment a good state of general nutrition and satisfactory renal excretion are favorable points in the prognosis whereas considerable splenic enlargement fever great tympanitic distention general hemorrhages edema of the legs the onset of ascites and its very rapid recurrence after tapping and the presence of complications have an ominous significance In adults a comparatively early age is favorable provided alcoholism can be completely stopped probably because the ability of the liver cells to undergo compensatory hyperplasia is higher than in more advanced life In children however prognosis is very grave According to Chauffard and Brodin[11] women having less resistance to alcohol are more prone to die from acute hepatic insufficiency men from ascites

Diagnosis

Diagnosis is not so easy as is often assumed The early symptoms resemble those of alcoholism and dietetic errors and the later manifestations those of grave intra abdominal often of malignant disease The history of dyspepsia of some considerable duration the presence of an enlarged liver and spleen and the occurrence of gastrointestinal hemorrhage not otherwise explained should suggest the disease and the subsequent occurrence of ascites strengthens the probability But the diagnosis has to be made from conditions characterized respectively by hepatic enlargement hematemesis and ascites and thus it is perhaps not surprising that in a series of eighty necropsy cases a correct diagnosis was arrived at in only thirty nine per cent (Cabot) Ottenberg Rosenfeld and Goldsmith[5] found Rosenthal s simplification of the tetrachlorphenolphthalein method of testing hepatic function valuable in the early diagnosis of cirrhosis

The differential diagnosis from the diseases presenting gastrointestinal hemorrhage and ascites has been referred to above The enlargement of the liver and spleen is an association compatible with syphilis or leukemia from which a diagnosis is helped by a Wassermann test and a blood count but the splenic enlargement in cirrhosis is very seldom such as to suggest leukemia Splenic enlargement is exceptional in malignant disease of the liver and the irregularity and size of the liver are much more prominent than in cirrhosis in which umbilication of the nodules is never present When the state of the liver is obscured by ascites in an emaciated patient particularly if jaundiced the diagnosis from intra abdominal malignant disease may be impossible until tapping makes it easier to examine the abdomen more completely and it must be remembered that primary carcinoma may supervene in a cirrhotic liver Enlarged glands above the clavicle or a tumor elsewhere are strongly in favor of malignant disea e but in a woman such an abdominal tumor may turn out to be a uterine fibromyoma

From the rare condition of Hanot s hypertrophic biliary cirrhosis difficulty

of diagnosis only arises in mixed cases of cirrhosis with an exceptional degree of splenic enlargement and jaundice These patients are usually young with a history of excessive alcoholism and the disease is rapidly progressive Cases of cirrhosis running a rapid febrile course have suggested hepatic abscesses or typhoid fever, but a blood examination should settle any doubt, leukocytosis would point to suppuration, and a positive blood culture or agglutination reaction to typhoid fever

Treatment of Portal Cirrhosis

Treatment falls under the following heads (1) To remove factors inducing the morbid change in the liver and so to prevent any further advance In the preascitic stage before hematemesis has occurred and in the presence of some hepatic enlargement and dyspepsia and a condition rather vaguely termed active congestion of the liver or hepatitis, the treatment is prophylactic It consists in absolute teetotalism, abstinence from highly spiced and irritating foods and measures to combat dyspepsia Spa treatment may be useful At a rather later stage the regime should be on similar but stricter lines, with milk, at any rate for a time as the basis of the diet Constipation and dyspepsia should be met by saline purges and minute doses of calomel Arsenic capsicum, and the tinctures and spirituous solutions of drugs should be avoided In the presence of a positive Wassermann reaction antisyphilitic treatment, especially a thorough course of iodides should be ordered In cases of cirrhosis referable to poisons or micro organisms provided by the spleen, excision of that organ is a logical if heroic form of prophylaxis In Egyptian splenomegaly good results follow splenectomy if performed before the hepatic cirrhosis has advanced so far as to cause jaundice or ascites (Richards and Day), but this disease is hardly comparable with ordinary cirrhosis

(2) The symptomatic treatment of hematemesis is as follows The patient should be kept completely at rest in bed, absolutely nothing should be allowed by the mouth for two or three days sucking ice should not be allowed but the mouth should be frequently washed out to relieve thirst which should be further combated by frequent saline enemas the first containing a drachm of calcium lactate to increase the coagulation time of the blood Emetin may be given hypodermically for its hemostatic effect and morphin if there be much mental disturbance Cautious feeding by the mouth can be resumed much sooner than in hematemesis due to gastric or duodenal ulcer

For ascites little reliance can be placed on attempts to remove the fluid by diuretics and purgation recently novasurol has been recommended for its use ee page 367 In some cases Karell s cure, namely a form of dry treatment in which nothing but 800 cc of milk in the 24 hours is allowed for two to four weeks has done good A chloride free diet has not fulfilled theoretical anticipation Paracentesis is palliative and should be performed when necessary, and

meanwhile iodides should be given Autoserotherapy or the injection into the abdominal wall of ascitic fluid has been reported by Vitry and Sezary[1 6] who introduced 3 drachms (12 cc) every other day to be followed by a urinary crisis and disappearance of the ascites possibly the drainage of the peritoneum into the subcutaneous tissues of the abdomen practised by Jaboulay Narath and Handley acts in the same manner

The surgical treatment by the production of vascular peritoneal adhesions around the liver and omentum (the Talma Morison operation and various modifications with the same end in view such as omentopexy) is an attempt to increase the compensatory anastomoses between the portal and the general circulations and has indeed been carried to its logical conclusion namely the performance of Eck s fistula by Vidal and Rosenstein [7] Probably however the beneficial effect is not so much due to short circuiting the portal circulation for this would increase the toxemia as to the improvement of the conditions (diminution of stasis) in the liver thereby enabling compensatory hyperplasia to take place and so lessening the toxemia The operation should if performed at all be done early on carefully selected cases and is contraindicated by well marked toxemia wasting considerable jaundice and definite cardiac or renal disease In 1906 Sinclair White [8] collected 227 cases with 37 per cent of cures and 13 per cent in which improvement was reported Out of 47 patients W J Mayo [9] reported that 21 were alive at various intervals after operation Eliot and Copp [10] prefer Schiassi s [11] method of omentopexy and obtained the best results in uncomplicated cases with large livers Splenectomy has been employed by Julhen [12] (7 cases with 2 operative deaths) W J Mayo (10 cases with 3 hospital deaths) Larrabee [133] (1 success out of 2 cases) and is disappointing

For vomiting due to gastritis temporary starvation alkalis bismuth and hydrocyanic acid may be tried Constipation should be treated by liquid paraffin or salines or in addition by a blue pill but powerful purgatives are inadvisable The drowsy comatose condition may be temporarily relieved by intravenous transfusion and acidosis should be combated by plenty of water by sugar and probably though opinion is rather turning against it bicarbonate of sodium Attempts to compensate for impairment of hepatic function by the administration of liver by the mouth or the injection of extract of liver (hepatin) hypodermically have been favorably reported on but the mechanism of success appears rather doubtful

(3) Measures to promote the compensatory mechanisms by means of which the disease becomes latent The surgical measures for increasing vascular adhesions (Talma Morison operation epiplopexy) have been mentioned when speaking of ascites There is no drug that can safely be employed in order to increase the hyperplasia of the liver cells arsenic is dangerous from its toxic effect on the liver cells

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SPECIAL FORMS OF CIRRHOSIS

Pigmented Cirrhosis

Cirrhosis of Hemochromatosis

Three forms of pigmented cirrhosis may be described cirrhosis of hemochromatosis malarial pigmentation of a cirrhotic liver, cirrhosis anthracotica The first of these cirrhosis of hemochromatosis, is described in Vol IV

Malarial Pigmentation of a Cirrhotic Liver

Although it would naturally be expected that the cellular necroses due to malarial infection would be succeeded by cirrhosis, and although various forms of malarial cirrhosis have been described, there is extremely little evidence that this sequence of events does occur But the same individual may suffer from cirrhosis and malaria and there may be an iron containing pigment derived from hemoglobin in the liver cells Kupffer s cells, and the fibrous tissues of the organ Cirrhosis in a malarial subject does not present special clinical features

Cirrhosis Anthracotica

Particles of carbon stone or metals absorbed from the alimentary canal, may be deposited in a cirrhotic liver It is analogous to the lungs of coal miners and has been described in miners charcoal burners, leather workers, and sweepers It is mainly of pathological rather than of clinical interest

Portal Cirrhosis in Children

Multilobular cirrhosis in children is rare among 16 100 necropsies at St George s Hospital during the 54 years 1865 to 1918 inclusive, there were only 12 cases under 21 years of age Among 90 cases under this age collected by Woolley 48 were males and 42 females the average age being 11 years in both sexes, whereas in adult life the disease is according to my figures, about three times commoner in males than in females and occurs some two years earlier in females

In some instances alcohol has been a factor but in others it can be definitely excluded The disease is occasionally familial thus I have notes of three children in a family, all of whom underwent laparotomy two for supposed tuberculous peritonitis and were found to have hobnailed livers Although the familial incidence may be due to precocious alcoholism or to irritating food such as fish soused in vinegar It is also compatible with the view that congenital

syphilis may play the disposing part of so diminishing the hepatic resistance that cirrhosis is induced by factors which normally would be harmless Another explanation of cases of cirrhosis in early life is that they are examples of subacute atrophy in which compensation and partial recovery have occurred but this does not explain the rare familial cases

The clinical features are generally speaking much the same as in adult life The hepatic and splenic enlargement is more prominent diarrhea more frequent and hematemesis less common The duration is shorter and the prognosis worse than in adults

There is a special group of cases with constant but latent cirrhosis called by S A K Wilson[13] progressive lenticular degeneration from the presence of bilateral symmetrical degeneration with later cavity formation in the lenticular nuclei The spleen is often enlarged and in 6 out of 30 cases examined after death there was pigmentation of Descemet s membrane of the cornea which at one time was thought to differentiate pseudosclerosis from Wilson s disease (Greenfield Poynton and Walshe) In 1921 Hall[136] collected 68 cases and proposed the name hepato lenticular degeneration it appears that this condition and Strumpell s pseudosclerosis are different clinical manifestations of the same disease The disease may be familial but not hereditary Paterson and Carmichael [7] recorded a form of familial cerebral degeneration chiefly affecting the lenticular nucleus in 12 children all slightly jaundiced after birth though the liver was normal Homen[138] and Yokoyama and Fischer[139] regarded it as due to congenital syphilis but Wilson discarding syphilis and alcoholism ascribed it to a toxin probably not microbic and possibly a lipoid which has a selective action on the lenticular nucleus analogous to that in the Kernicterus in the physiological jaundice of the new born Possibly the toxin is formed in the liver It may be mentioned that chronic manganese poisoning produces some of the symptoms of paralysis agitans and biliary cirrhosis (Findlay [1 0]) The clinical features are bilateral tremor and spasticity dysarthria dysphagia eventually contracture and emaciation the disease is slowly progressive and terminates fatally in from four months to two or four years

Biliary Cirrhosis

In this group of cirrhoses the predominant clinical feature is jaundice thus contrasting with portal cirrhosis in which the symptoms are specially connected with *the portal circulation*

Hypertrophic Biliary Cirrhosis

Synonyms — Hanot s disease Hanot s cirrhosis

Definition — A disease characterized by chronic jaundice periodic attacks of abdominal pain and fever enlargement of the liver and spleen absence of

ascites and by its preference for the young There is no gross obstruction to the bile ducts and histologically the cirrhosis is more unilobular than in portal cirrhosis

Incidence of Hypertrophic Biliary Cirrhosis

The disease is certainly rare, and as it may be closely imitated by portal cirrhosis with an acute onset and a mixed form of fibrosis, by syphilis and by chronic splenomegalic hemolytic jaundice, considerable doubt has been expressed as to its existence as a separate disease Thus, of cases with the characteristic clinical features some may be found after death to show multilobular cirrhosis and others may give a positive Wassermann reaction (Castaigne[141]) As the morbid appearances frequently show a combination of multi and unilobular cirrhosis they have been regarded as insufficient to justify this special form of cirrhosis (Oertel[14]) This difficulty may perhaps be removed by the consideration that cirrhosis, wherever it begins, has a tendency to spread and that in the kidneys a tubal nephritis which may be regarded as corre ponding to a biliary cirrhosis becomes complicated in time by interstitial nephritis Further, it has been shown experimentally (Rous and Larimore[143]) that the changes induced in the liver differ according to the level in the biliary tract where the obstruction is situated (See p 391) Although there are other difficulties, such as our ignorance about its cause, the transitional forms to portal cirrhosis and the varieties of the disease it seems advisable to give an account of Hanot s cirrhosis as distinct from multilobular cirrhosis

Various forms of the disease have been described by Chauffard[144] Gilbert[145] and Lereboullet[146] mainly on the basis of the relative size of the liver and spleen In the ordinary form described by Hanot[14] in 1875 both organs are considerably but equally and synchronously enlarged in the splenomegalic form the splenic enlargement is specially predominant in the hypersplenomegalic form the spleen is actually bigger than the liver, in the metasplenomegalic variety the splenomegaly appears before the hepatic enlargement whereas in the presplenomegalic form the liver is first enlarged In the hepatomegalic or microsplenomegalic form the hepatic enlargement is the striking feature, and in atrophic biliary cirrhosis the liver is small Gilbert and Fournier[148] described a special juvenile type with great splenic enlargement

Etiology of Hypertrophic Biliary Cirrhosis

The disease usually appears under the age of thirty and a considerable proportion of the cases occur in childhood Males are rather more often attacked It may be familial and even hereditary There is no reason to believe that alcoholism is a causal factor indeed the infection has been thought to be water borne and the disease has followed typhoid fever Malaria syphilis and tuberculosis cannot be held responsible

Pathogeny of Hypertrophic Biliary Cirrhosis

It was originally thought to be due to an ascending infection of the bile ducts from the duodenum but the freedom from duodenal catarrh and the complete absence of suppuration which might be expected to supervene if this were the case are against this hypothesis Further there is little in the way of ordinary chronic interstitial pancreatitis which should be present on the assumption of an ascending infection The fever and the concomitant enlargement of the spleen and sometimes of the lymphatic glands favor the view of infection or toxemia by the hepatic artery As the result of this hemic infection or toxin the small bile ducts may be inflamed in a manner analogous to that in experimental poisoning by toluylenediamin the process beginning in the biliary radicles The French School have denied the existence of intrahepatic cholangitis and consider the jaundice due to change in the hepatic cells Although bacillus coli the pneumococcus and a diplococcus have been thought to be the causal organism no certainty on this question has been reached Experimentally manganese which is mainly excreted in the bile gives rise to biliary cirrhosis (M Findlay [140]) and Casamayor has reported biliary cirrhosis in a fatal case of manganese poisoning in man

Morbid Anatomy of Hypertrophic Biliary Cirrhosis

The liver is much and usually uniformly enlarged weighing from 2 500 grams up to as much as 3 800 grams The surface is finely granular dark green in color and may show some adhesions to the diaphragm The blood vessels and larger bile ducts are healthy and bilirubin-calcium calculi very rare Gall stones are only occasionally found in the gall bladder On section the liver is firm and from the fine mesh of the cirrhosis has the aspect of granite

Microscopically there is a delicate fibrosis surrounding the individual lobules and the small bile ducts some of which are obliterated and others dilated The bile capillaries may contain plugs of bile Around the periphery of the lobules there are the striking pseudobile canaliculi which stain brilliantly and are composed of cubical or elongated cells enclosing a potential lumen The liver cells are comparatively free from morbid changes These appearances are best seen in an early stage and it is noteworthy that Hanot s original description was based on cases prematurely fatal from some intercurrent disease In cases running their full course multilobular cirrhosis very possibly from poisons manufactured in the spleen supervenes and complicates the picture

The spleen is much enlarged commonly weighing from 500 to 1,300 grams and may be larger than the liver There may be peri plenic adhesions Microscopically there is fibrosis distention of the sinuses with blood and endothelial

proliferation of the pulp The periportal lymph glands are enlarged and pigmented The alimentary canal is free from inflammation, but the pancreas shows a fine fibrosis of the embryonic type All the organs are bile stained

Clinical Picture of Hypertrophic Biliary Cirrhosis

The onset is gradual and some malaise abdominal discomfort or pruritu may precede the appearance of jaundice which generally first brings the patient under medical observation when physical examination shows considerable enlargement of the spleen The first symptoms may be gastrointestinal with dyspepsia vomiting abdominal pain diarrhea, hepatic pain and jaundice, or splenic pain The course is slow and often for years the general health is fair except for periodic attacks of fever abdominal pain, and increase in the jaundice, and in hepatic and splenic enlargement These crises become more frequent and the patient loses ground Digestion is much less disturbed than in multilobular cirrhosis but attacks of diarrhea are easily set up Hematemesis is rare and like ascites occurs only when multilobular cirrhosis has supervened as a late result The stools contain bile pigment the urine is constantly bilious, usually copious free from albumin sugar and urates as the liver cells are well preserved at any rate for a long time alimentary glycosuria cannot be induced by the administration of 100 grams of glucose The blood shows a slight secondary anemia with the color index below one There may or may not be a leukocytosis In the later stages biliary toxemia may cause hemorrhages from the gums nose and throat The heart may be dilated and hemic or systolic mitral murmurs may be audible

The jaundice is slight at first but progressive, eventually becoming dark green and as mentioned above it increases during the periodic exacerbations There is in addition a melandodermia which though generally combined with the jaundice may precede it Pruritus may be troublesome and the resulting scratching may lead to an eczematous or lichenous eruption As in other cases of prolonged jaundice xanthoma may occur The patients are thin, poorly developed and in children the arrest of development is seen in infantilism In long standing cases especially in the young the terminal phalanges of the fingers and toes become bulbous like the end of a spoon Skiagraphy shows that these Hippocratic fingers are not due to bony enlargement, but in some instances there is in addition definite bony enlargement of the ends of the long bones, Marie s hypertrophic osteoarthropathy I have seen mild peripeheral neuritis with numbness of the fingers but this appears to be exceptional

The abdomen is somewhat distended the right hypochondrium being usually prominent Distention of the subcutaneous veins is rare A feeling of weight and discomfort is common and attacks of colic may occur The liver is uniformly enlarged extending down to or below the umbilicus and is smooth and generally though slightly tender The gall bladder is not palpable The spleen

is much enlarged and smooth Attacks of perisplenitis may cause pain and friction audible with the stethoscope The hepatic and splenic enlargements are progressive and as already pointed out increase during the periodic exacerbations The relation between the hepatic and splenic enlargements varies in the different forms mentioned above but from the greater distensibility of the spleen in early life the enlargement is usually more pronounced in children Occasionally the lymphatic glands in the axillae and groins are palpably enlarged

Termination and Prognosis

In uncomplicated ca es death may be due to gradually increasing toxemia but suddenly acute degeneration of the liver cells resembling that in acute yellow atrophy may precipitate coma and death Erysipelas is especially prone to attack these patients who may also succumb to other acute infections such as pneumonia or peritonitis The disease is incurable and apparently never arrested but life may be prolonged for ten years or even longer the average duration being five years In some instances the disease runs a relatively acute course in two years The outlook is governed by the patient s circumstances exposure to cold and wet being injurious influences and by the general state of nutrition The occurrence of exacerbations at shorter intervals as indicating that the disease is advancing rapidly and the incidence of complications render the prognosis very grave but recovery from erysipelas may occur if the urinary excretion is well maintained Widespread hemorrhages edema of the legs and ascites show that the end is approaching

Diagnosis of Hypertrophic Biliary Cirrhosis

The presence of chronic progressive jaundice with periodic febrile exacerbations accompanied by increase in the considerable hepatic and splenic enlargement with constant bile in the urine and in the feces without any evidence of gallstones or cholecystitis especially in a young person suggests the di ease

Acute multilobular cirrhosis with jaundice and well marked hepatic and splenic enlargement runs a rapid course In multilobular cirrhosis with jaundice the splenic enlargement is not so great and the jaundice usually transient but it must be admitted that the diseases are sometimes combined and that transitional cases occur Syphilis sometimes imitates Hanot s disease and a Wassermann reaction should always be carried out to prevent this confusion In calculous obstruction of the common bile duct jaundice may be associated with an enlarged liver but there is no corresponding splenometaly In chronic splenomegalic hemolytic jaundice the liver is either not enlarged at all or very slightly the red blood cells show fragility the urine is free from bile and pruritus xanthoma and interference with physical development do not occur In Banti s

disease or the terminal hepatic cirrhosis of chronic splenic anemia, resemblance will occur only when there is jaundice in that event the history of the occurrence of recurrent gastrointestinal hemorrhages should prevent a mistake In rare instances massive tuberculosis of the liver and spleen may cause chronic jaundice and imitate the disease

Treatment of Hypertrophic Biliary Cirrhosis

Treatment is mainly directed to maintaining the general health Exposure to cold and wet should be avoided but fresh air and sunlight are desirable The diet though simple should be more generous than in ordinary portal cirrhosis, but alcohol should be forbidden Pruritus may require applications such as carbolic acid 1 in 60 lactate of calcium, or thyroid extract internally, or small injections of pilocarpin Intestinal flatulence may be met by calomel 1/20 gr (0 003 gm) three times a day or in larger but less frequent doses so as to combine its purgative and antiseptic properties Good results have been reported from drainage of the gall bladder (Greenough [149]), but the question arises whether or not some of these cases were examples of infective cholecystitis Out of twelve cases submitted to splenectomy W J Mayo [150] reported one death in the hospital and five alive at various intervals

Endemic Biliary Cirrhosis in Infants

Endemic biliary cirrhosis in infants has been described in India, especially in Calcutta chiefly among Hindus as an extremely fatal disease killing off ninety five per cent of those attacked during the first two years of life It begins about the seventh month of life with fever and enlargement of the liver and spleen There is at first a unicellular cirrhosis which subsequently becomes unilobular It has been thought to be due to toxic bodies in the food, especially as the nursing mothers restrict themselves to a dry diet and take a decoction of black pepper, but Castellani and Chalmers suggest that it is kala azar

An endemic form of unicellular cirrhosis with hepatic enlargement jaundice, and continued fever, but without splenomegaly was described in 1897 by Carmono y Valle [151] in Mexico Ascites is often present, and the disease runs a rapid course in six to eight months

Obstructive Biliary Cirrhosis

Obstructive biliary cirrhosis consisting in fibrosis preading out from and due to obstruction of the bile ducts has caused much debate Experimental ligature of the ducts has given rather varying results From numerous experiments with various modifications on rabbits Rous and Larimore [143] find that a

septic obstruction involving the larger bile ducts causes a stellate fibrosis around them obstruction of the small bile ducts in the portal spaces, a pure unilobular cirrhosis, and obstruction of the intralobular bile canaliculi leads to a diffuse intralobular cirrhosis The diversity of the hepatic changes depends on differences in the duct levels at which the injurious factor is active McMaster and Rous[1] have also shown that obstruction of the common duct when the gall bladder is able to perform its concentrating action leads to distention of the intrahepatic ducts with thick tarry bile whereas when the gall bladder is functionless the fluid distending the ducts is white bile and the condition may be described as a manifest hydrohepatosis

In man infective cholangitis such as that set up by gall stones certainly produces a pericholangitic cirrhosis On the other hand aseptic obstruction of the common bile duct for example by carcinoma of the head of the pancreas is very rarely associated with cirrhosis of the liver although it causes dilatation of the intrahepatic bile ducts icteric necrosis and atrophy of the liver cells In gall stone obstruction of the common duct the results are not so constant in some instances cholangitis and pericholangitic fibrosis are present in others the liver resembles that in aseptic obstruction of the ducts by a growth The hepatic cirrhosis associated with congenital obliteration of the ducts has been regarded by John Thomson Beneke Ford[5] and Lavenson as due to the obstruction of the ducts but, as pointed out elsewhere the obstruction of the ducts may be secondary to a descending inflammation from the small intrahepatic ducts which is responsible for the cirrhosis To sum up biliary obstruction per se does not constantly cause any form of cirrhosis from a study of 184 cases of cirrhosis ascribed to obstruction Mangelsdorf[1,4] found that there was no constant form of cirrhosis

Clinical Picture of Obstructive Biliary Cirrhosis

When cirrhosis whether portal or pericholangitic is associated with biliary obstruction the manifestations are those of biliary obstruction with jaundice The liver is palpably enlarged from distention with bile and hard but not so greatly enlarged as in Hanot s cirrhosis and the spleen is not palpable From the atrophy and functional impairment of the hepatic cells cholemia or biliary toxemia is likely to occur

Prognosis and Treatment

The prognosis of cirrhosis associated with biliary obstruction is inseparable from that of the obstruction In gall stone impaction operation may if the hepatic changes be not too far advanced be followed by recovery But considerable enlargement of the liver is a bad sign In malignant obstruction of the ducts the chance of benefit from operation is very slight though it is open

to discussion whether a palliative operation, such as drainage of the gall bladder to remove the jaundice, is advisable or not In the cirrhosis associated with congenital obliteration of the ducts death usually occurs within the first eight months of life

The treatment is that of obstructive jaundice by operation or palliative means (see Chap VII) Ascites should be treated as in portal cirrhosis

Tuberculosis of the Liver

The clinical manifestations of hepatic tuberculosis, in contrast to those of syphilis are of subordinate importance though pathologically they are of much interest

The path of infection varies During fetal life tuberculous disease of the placenta may be responsible for the passage of tubercle bacilli by the umbilical vein to the liver and in this way produce the rare instances, of which Hale White[1 5] could only collect six cases, of tubercles observed there within the first two weeks of life In generalized tuberculosis the hepatic artery carries tubercle bacilli to the liver and this probably also occurs in cases that fall short of fatal generalized tuberculosis The portal vein conveys bacilli in cases of intestinal tuberculosis in so called primary tuberculosis of the spleen the liver is infected in 80 per cent of the cases (Winternitz[1 6]) the tubercle bacilli travelling by the splenic branch of the portal vein The evidence is against an ascending infection of the common bile duct from the duodenum The spread of tuberculosis into the liver by the lymphatics of the capsule in general tuberculous peritonitis or by the lymphatics of the portal fissure when the lymphatic glands are infected is very slight Although miliary tubercles are common the liver seems to inhibit the further growth of the microorganism The forms of hepatic tuberculosis are (1) miliary (2) tuberculosis involving the bile ducts, and (3) massive tuberculomas and abscesses

Miliary Tuberculosis of the Liver

Miliary tubercles are very common in tuberculosis Simmonds found them in 82 per cent of 476 cases of tuberculosis, 76 per cent in adults, and 92 per cent in children Zehden found miliary tubercles in the liver in 50 per cent, Torry in 63 per cent and C Y White[157] in 80 per cent of all cases of fatal pulmonary tuberculosis thus corresponding fairly well with the post mortem incidence of intestinal ulceration in the disease The tubercle bacilli may then reach the liver (a) directly by the portal vein (b) by the roundabout route of the lymphatics the thoracic duct the veins and after traversing the lungs, the hepatic artery or (c) directly from the tuberculous foci in the lungs by the arterial blood stream

There are no constant clinical signs or symptoms of miliary tubercles in the

liver though the liver may be somewhat enlarged In rare instances jaundice is associated and from the presence of large numbers on the capsule and the resulting peritonitis there may be a friction rub

Tuberculosis Involving the Bile Ducts

This form also called tuberculous cholangitis and pericholangitis is not very common It is due to tuberculous infection of the portal spaces conveyed from the intestines by the portal vein and as already mentioned there is no satisfactory proof that tuberculous infection spreads up the common bile duct When the tuberculous granulation tissue undergoes caseation the appearance produced resembles that of lymphadenoma in the portal spaces microscopical examination may be necessary to distinguish this stage from the rare condition of chronic nontuberculous pericholangitis The caseous matter softens down and after perforating into the previously healthy bile ducts becomes bile stained

The clinical picture is that of abdominal pulmonary or generalized tuberculosis and it is remarkable that jaundice is practically always absent Attacks of abdominal pain probably due to tuberculous ulceration of the intestines or peritonitis may occur and ascites may be present The condition can hardly be diagnosed and there is no special treatment

Massive Tuberculoma of the Liver

Massive tuberculomas which from caseation and the presence of a fibrous capsule present some resemblance to gummas are rare As tubercle bacilli have not been isolated from all the cases (Clement[1 8] Moore[169]) the possibility that some of these caseous masses are due to infection other than that of tuberculosis must be borne in mind

Clinically there is usually irregular fever epigastric pain and hepatic enlargement In some instances a tumor may be palpable suggesting malignant disease as in Thayer's [0] case The spleen may be palpable and the diagnosis from typhoid fever may arise and should be settled by laboratory tests Jaundice may supervene The prognosis is grave as these tuberculomas are commonly multiple but their removal has been successfully carried out in some cases

A *tuberculous abscess* may result from softening down of these massive tuberculomas and may be either inside the liver or by perforating appear as a perihepatic or subphrenic absce s Such a tuberculous abscess may be single Multiple tuberculous abscesses are usually small and belong to the group of cases of tuberculosis involving the bile ducts If a caseous tuberculoma opened into a bile duct it would be difficult to distinguish it from the pericholangitic category of cases

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only are of this nature it is probable that the majority are due to placental infection of the fetus In post natal syphilis in infants such as may be con tracted from a wet nurse the disease is the same as in the acquired form Congenital syphilis of the liver will be considered under the two heads of the ordinary early and the delayed manifestations

The Ordinary Hepatic Manifestations of Congenital Syphilis

Morbid Anatomy — The appearances of the liver vary there may be little change to the naked eye although microscopical examination shows diffuse change Fetal peritonitis may cause perihepatic adhesions but otherwise the surface is smooth Usually the liver is enlarged tough on section and altered in color being dark red and congested in the early stages and yellowish or brownish gray mottled shiny or flint colored later on and may then suggest amyloid change Small sago like granulomas or miliary gummas are not un common but caseous gummas are exceptional In rare instances there are local ized masses of fibrous tissue forming tumor like masses

The spleen is enlarged fibrosed and firm There may be peritoneal adhe sions but gummas are very rare The pancreas testes and kidneys may show small-celled infiltration and there may be changes in the lungs

The *clinical features* are those of congenital syphilis with enlargement of the liver and spleen the latter being an index of the severity of the disease The liver is enlarged in about half the cases of congenital syphilis but it must be remembered that the infant s liver normally projects further down than in adult life The organ is firm sometimes tender and in rare instances presents a tumor like formation Jaundice is probably not so rare as is usually stated some writers such as Thomson deny that it is due to unicellular cirrhosis alone others regard it as depending on changes in the small bile ducts but it may also be due to secondary infection with B coli and B proteus to changes re sembling those of acute atrophy or to chronic hemolytic jaundice Usually it is present at birth and in rare instances may intermit The stools contain bile and this may assist in the diagnosis from syphilitic obstruction of the common bile duct an extremely rare condition Ascites is very rare but may occur in intra uterine life from peritonitis and is of very grave prognosis

The *diagnosis* rests on hepatic enlargement in an infant with other evidence of congenital syphilis or a positive Wassermann reaction

The *prognosis* depends on the general condition and on the degree of visceral enlargement A considerable number of infants with the disease are still born or die soon after birth The incidence of any secondary infection renders the outlook very serious

Treatment — By way of prophylaxis a pregnant syphilitic woman should be given antisyphilitic treatment and after the child is born this should be con tinued e pecially if she be suckling the infant The child should be treated by

Relation of Tuberculosis to Hepatic Cirrhosis

Tuberculosis and cirrhosis may occur in the same liver, and tuberculosis, particularly of the lungs, may be associated with hepatic cirrhosis but without hepatic tuberculosis In some cases the tuberculosis is obviously of later date than the cirrhosis, in other cases the question arises how far local destruction of liver cells, either by tubercle bacilli or by toxins from extrahepatic foci of tuberculosis and the resulting fibrosis may go in the direction of inducing ordinary cirrhosis The finding of tubercle bacilli in the ascitic fluid of cirrhosis of the liver has been mentioned under the heading " pathogeny of portal cirrhosis In guinea pigs avian tubercle bacilli produce hepatic cirrhosis and Hanot [161] ascribed deep scarring of the human liver, resembling that of syphilis, to tubercle bacilli and also to their toxins absorbed from pulmonary lesions Lavenson and Karsner [16] also found some periportal fibrosis in 48 or 96 per cent, of 50 cases of tuberculosis of various parts of the body, a much higher percentage than in a number of controls But in man the tubercle bacillus and its toxins usually produce more degenerative changes in the liver cells than reactive lesions in the interstitial tissues It seems reasonable to conclude that although some multilobular cirrhosis may be secondary to tuberculosis in the liver or elsewhere genuine cirrhosis of clinical importance is not often thus induced Cirrhosis in cases of miner's phthisis " may be due to the silica

SYPHILIS OF THE LIVER

Apart from the question as to the relation of syphilis to ordinary portal cirrhosis the hepatic manifestations of syphilis will be considered under the heads of (1) congenital (a) early and (b) late or delayed, and (2) acquired (a) acute or secondary and (b) chronic or tertiary

Congenital Syphilis of the Liver

The liver is affected in a large percentage of infants with congenital syphilis, thus contrasting with the acquired form of the disease By the term hereditary syphilis is meant infection of the ovum by the spirocheta pallida conveyed by the spermatozoon in this event the ovum would probably be destroyed early, but if it survived, spirochetes would reach the liver by the hepatic artery as in the acquired disease, and therefore the liver would not be specially prone to infection In congenital syphilis on the other hand, the fetus receives the spirochetes from the maternal placenta by the umbilical vein, and the liver, being the first organ to filter the infected blood is damaged in a high proportion of the cases Although it is possible that syphilis is occasionally hereditary in the sense mentioned above and that some of the cases manifesting symptoms at a late stage

Acquired Syphilis of the Liver

Liver Changes in Acute or Secondary Syphilis

Before the era of arsphenamin the administration of which may be followed by jaundice in 0 4 to 0 6 per cent of the cases treated (Harrison[165] Milian) benign jaundice was recognized as occurring during the secondary and roseolou stage in a small number of cases among 23 261 cases obtained by combining the statistics of Werner and Goldstein it occurred in 77 or 0 3 per cent But I believe that it is not so rare as this It has been explained in various ways as due to a change in the mucosa of the ducts analogous to the cutaneous roseola to inflammation of the mall bile ducts which is associated with an intercellular infiltration resembling that in the congenital form of the disease and actually seen in some cases of the acquired disease accidently fatal at this stage to a condyloma of the bile ducts to pressure exerted by enlarged glands in the portal fissure to be hemolytic and due either to a hemolysin or to increased fragility of the red cells or at the present time to functional disturbance cau ed by changes in the liver cells (Langevin and Brule[166] Arden Delteid Derrien and Azoulay[167])

The onset is usually sudden but without the disturbance of digestion or the pain characteristic of catarrhal jaundice or gall stones respectively It appears from five weeks to six months after infection and tends to persist unless treated by antisyphilitic measures The liver is usually slightly enlarged and the spleen may be palpable The urine is free from bile

The prognosis is good provided appropriate treatment is employed but in a few cases acute yellow atrophy supervenes

Liver Changes in Chronic or Tertiary Syphilis

The chronic or tertiary lesions of syphilis in the liver include (1) the focal gumma and its resulting cicatrices (2) diffuse changes of amyloid disease and fibrosis and (3) a combination of the focal and diffuse changes

Although well recognized hepatic gummas are not common and are rarer than syphilitic cicatrices out of 43 148 necropsies obtained by combining the figures from Guy s Hospital (Hale White) St George s and Middle ex Hos pitals Philadelphia Hospital (Flexner[168]) and the Johns Hopkins Hospital there were 151 or 0 35 per cent with gummas whereas among 28 548 nec ropsies at Guy s St George s and Philadelphia there were 144 or 0 5 per cent with cicatrices But gummas are more often found in the liver than in any other organ

Males are more often affected than females this would be a natural result of the greater frequency of syphilis in men There is some reason to accept the

intravenous injection of arsphenamin, the veins of the scalp being a convenient site and by mercurial inunctions. Neoarsphenamine may be used intramuscularly. (See article on congenital syphilis.) The intramuscular injection has the advantage of the ease with which it is given; it is effective and safe (Boone and Weech [163])

Late or Delayed Congenital Syphilis of the Liver

Delayed congenital syphilis of the liver, in which the symptoms do not appear until years have passed, is rare and consists in the lesions of tertiary syphilis in the adult with a special liability to amyloid disease. Jaundice is rare but ascites is common and may be due to chronic exudative peritonitis spreading from the viscera (Acuna and Casaubon [164]). The liver is enlarged and there may appear to be a tumor. The spleen is enlarged. There may be widespread endarteritis obliterans so that the pulse cannot be felt in the limbs, and it is not improbable that some cases of mitral stenosis are of this nature. The subjects are badly developed and may show infantilism. There is a considerable liability to secondary infections such as erysipelas.

The *diagnosis* from syphilis acquired in early life depends on the presence of some stigma of congenital syphilis, such as interstitial keratitis, Hutchinson's teeth, bilateral effusion into the knee joints. From portal cirrhosis in a child, formerly the subject of congenital syphilis, the diagnosis may be very difficult. From sarcoma and hydatid disease of the liver and Banti's disease other evidences of syphilis and particularly the Wassermann reaction should establish the diagnosis.

Prognosis is much graver than in early congenital syphilis. Death may be due to secondary infections, uremia, cardiac failure, asthenia, or hemorrhage from an esophageal varix.

The treatment is that of tertiary hepatic syphilis in the adult.

Portal Cirrhosis in Congenital Syphilis

Portal cirrhosis is occasionally found in the bodies of children with well marked stigmata of congenital syphilis, and it is reasonable to believe either that syphilis may cause ordinary portal cirrhosis, or that the disappearance of intercellular cirrhosis leaves the liver unduly susceptible to the causal factors of portal cirrhosis. The diagnosis from late congenital syphilis of the liver is difficult, but in both instances the outlook is very serious.

malignant disease of the liver on the other hard failure of anti syphilitic treatment does not prove that the condition is due to some condition other than syphilis for cirrhosis cicatrices, or a thrombosed vein will not be affected by antisyphilitic treatment But probably many reputed cures of portal cirrhosis are due to anti leutic treatment of patients with hepatic syphilis

Cases with the Symptoms of Amyloid Disease —The liver may be much enlarged from the combined effects of gummas and amyloid disease the spleen of considerable size and the urine albuminous When dropsy is present the clinical picture may suggest renal disease especially if ascites obscures the hepatic and splenic enlargement

Cases Imitating Malignant and Other Tumors of the Liver —Cases of this group are not uncommon the liver may be greatly and generally enlarged there may be multiple nodules or a rounded tumor the emaciation and pain may be considerable Signs of syphilis such as skin eruptions may give a clue but a Wassermann reaction should always be carried out Concomitant splenic enlargement is rare in malignant disease and common in syphilis and albuminuria from amyloid disease of the kidneys is in favor of syphilis Syphilitic and malignant disease of the liver may be combined so that a positive Wassermann reaction though highly suggestive i not conclusive It has moreover been stated that a positive Wassermann reaction may occur in malignant disease of the liver without any other evidence of syphilis (Verdozzi and Urbani[11]) Difficulty may arise in distinguishing a hydatid cyst embedded in the liver from gummatous infiltration of a lobe but assistance may be obtained by the test for deviation of the complement for hydatid infection

Cases with Fever Resembling Hepatic Suppuration —Fever is common in hepatic syphilis among McCrae s 56 cases it was noted in 49 or 87 5 per cent In rather infrequent cases its character strongly suggests hepatic abscess pylephlebitis malaria typhoid fever lymphadenoma or tuberculosis The possibility of secondary infection of a gumma should be borne in mind in cases with a history of a positive Wassermann reaction but this appears to have been rarely established The presence of leukocytosis is against syphilis for in 30 of McCrae s cases the average white count was 8 400 Trabaud s case showed 8 per cent of eosinophils In this syphilitic fever iodides and mercury usually exert a dramatic effect

Cases with Jaundice or Suggesting Gall Stones —Slight jaundice of the conjunctivae is not uncommon but general jaundice is usually regarded as rare though it occurred in 23 or 41 per cent of McCrae s 56 cases A gumma in the portal fissure may cause obstructive jaundice which will yield to antisyphilitic treatment, but the jaundice due to cicatrix will be permanent In rare instances of this jaundice there are attacks closely simulating biliary colic In such a case with definite evidence of syphilis a course of vigorous antisyphilitic treatment should be tried A calculous gall bladder with an adjacent gumma has imitated carcinoma of the gall bladder (Wakeley[12])

obvious view that insufficient early treatment is a factor (Tallquist[169]) Trauma probably favors the development of gummatous change

Gummas and cicatrices are usually multiple, I have seen as many as 268 gummas in one liver they are said to be specially frequent close to the falciform ligament From a large number of scars and the resulting atrophy and compensatory hypertrophy, the liver may become greatly distorted botyroid or lobate Among 174 collected cases of hepatic gummas 11 per cent were combined with amyloidosis The combination of gummas, cicatrices and amyloid disease may produce a tumor like formation of the liver A gumma or cicatrix in the portal fissure may involve the portal vein or by compressing the bile ducts cause jaundice The symptoms therefore depend very much on the position of the gumma

The Clinical Manifestations of Tertiary or Chronic Syphilis of the Liver

Symptoms usually appear after a considerable interval — even as long as twenty or thirty years — from the original infection, though in some cases they are seen within three years and exceptionally still earlier From analysis of 134 cases of hepatic gummas (Allen's and McCrae's[170] figures combined) it appears that 89 or 66 4 per cent were found in patients between 30 and 50 years of age But often hepatic syphilis is quite latent during life The general symptoms may be mentioned first loss of weight is frequent and emaciation may be considerable some degree of fever is common and may suggest tuberculosis there is some anemia without leukocytosis, and abdominal pain and tenderness, discomfort or dyspepsia often cause complaint The symptoms vary much and the following groups may be considered from a diagnostic point of view

Cases with Ascites Imitating Cirrhosis and Chronic Peritonitis — At the present time when it is doubtful how far syphilis is responsible for portal cirrhosis, the diagnosis during life between portal cirrhosis in a patient with a positive Wassermann reaction on the one hand and gummatous disease of the liver on the other hand is extremely difficult Ascites requiring tapping is not uncommon in hepatic syphilis and stress has been laid on its intermittent character (McCrae) It may be due to chronic syphilitic peritonitis, perihepatitis over gummas pressure on the portal vein or its branches by gummas or adhesions and in rare instances to portal thrombosis or constriction of the hepatic veins As in cirrhosis concomitant enlargement of the spleen often occurs, this was so in 54 or 63 per cent of McCrae's 85 cases Hematemesis from varicose esophageal or gastric veins is rare but may prove fatal The hepatic enlargement is less uniform than in cirrhosis and the left lobe is often unduly prominent

In making a diagnosis a positive Wassermann reaction must carry great weight, but is not conclusive as syphilis does not of course protect against

some weeks as the beneficial effect may not be achieved at once Iodides cause absorption of a gumma by fixing the antitryptic ferments and thus allowing the autolytic tryptic ferments to dissolve the caseous material Intravenous injections of arsphenamin may be given cautiously beginning with small doses, o or o 3 gram twice a week If there be anemia iodide of iron may be given The patient s general health should be improved in every available way Alcohol is best avoided

When in an exploratory laparotomy a large gumma is discovered or in rare instances in which a gumma is ulcerating through the abdominal wall the removal of its caseous contents is advisable as tending to hasten the cure But otherwise operation should never be advised until medical measures have had an extended trial

Actinomycosis of the Liver

This disease (see Vol V Chap XXIV) is very likely to escape recognition and so is probably less rare than it is thought to be In 1903 Auvray[179] could only collect 32 cases of hepatic actinomycosis out of 109 British cases analyzed by Acland[180] in 1907 there were 32 in the liver and during the ten years 1902–1912 there were 11 cases in six London hospitals In 20 out of Aribaud s 30 cases the hepatic infection was regarded as secondary to the intestine in such cases there is usually infection near or of the vermiform appendix and from thence it spreads by the blood stream or by continuity to the liver Kellock[181] however argued that even in cases with disease of both the intestine and the liver the two infections are independent the ray fungus working its way up the bile duct from the duodenum In exceptional cases the primary focus has appeared to be in the female genital organs or the jaw

The liver in actinomycosis is enlarged with adhesions on the surface and on section the actinomycotic tissue has a characteristic honeycombed appearance compared to a sponge soaked in pus The process tends to spread irrespective of the ordinary boundaries of the organ and may cause a retroperitoneal abscess empyema or open on the body wall or into the stomach

Clinically signs pointing to the liver may be preceded by abdominal symptoms from intestinal infection The fever and hepatic enlargement may suggest an ordinary abscess or the signs may lead to a diagnosis of perinephric abscess or an empyema There is leukocytosis Jaundice is very rare and ascites exceptional

The *prognosis* is very grave all Duvau s[18] forty cases terminated fatally The occurrence of secondary infections as in tuberculosis is the factor determining the gravity of the outlook for then iodides fail to exert a beneficial effect

The *diagnosis* depends on the recognition of the fungus in the pus This may be easy when the characteristic granules, visible to the naked eye are discharged but in other cases many examinations may be necessary before it is

Cases Resembling Hanot's Cirrhosis — These are rare, but certainly occur (Hanot Castaigne) There may be gross evidence of syphilis elsewhere, or a positive Wassermann reaction may be the only diagnostic clue (Castaigne[1 4])

Cases Resembling Chronic Splenic Anemia and Banti s Disease — In some instances the spleen is much enlarged and the liver though showing gummatous change is not clinically affected, or when somewhat enlarged is much less so than the spleen the first category resembles the chronic splenic anemia of adults in which there are recurrent gastrointestinal hemorrhages, anemia of the chlorotic type, leukopenia, and splenomegaly, and the second imitates Banti s disease in which hepatic cirrhosis and ascites supervene on splenic anemia A positive Wassermann reaction strongly suggests syphilis and the corresponding method of treatment which however, may be disappointing, Weil[1] reported seven such cases of splenomegaly with a positive Wassermann reaction in which antisyphilitic treatment did not do good and in some instances was apparently harmful and he suggests that the Wassermann reaction is due to some unknown parasite It is conceivable that there is a secondary infection present and that in such cases antisyphilitic treatment fails, just as iodides do in actinomycosis when complicated by pyogenic infection In some such cases antisyphilitic treatment has not succeeded until splenectomy has been done (French and Turner[1 6], Hartwell[1 7] Giffin[1 8])

Diagnosis of Hepatic Syphilis

The diagnosis of hepatic syphilis depends on the detection of other signs of syphilis the Wassermann reaction, and the therapeutic test by antisyphilitic remedies

Prognosis

The prognosis of gummatous disease of the liver, if efficiently treated, is much better than that of some of the conditions it may imitate, such as malig nant disease and cirrhosis On the other hand, cicatrices and fibrosis are not likely to be affected and therefore hepatic enlargement is more likely to be cured than jaundice and ascites which may be due either to cicatrices or to gummas, though in the latter event the jaundice and ascites may rapidly dis appear

Treatment

Full doses of iodides and mercurial inunction should be employed The three iodides of potassium sodium and ammonium may be given, or the potas sium salt in combination with spiritus ammoniae aromaticus The initial dose of the iodides should be 15 grains (1 gm) three times a day before food, and should be increased until double this amount is reached, and continued for

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Clinically signs pointing to the liver may be preceded by abdominal symptoms from intestinal infection The fever and hepatic enlargement may suggest an ordinary abscess or the signs may lead to a diagnosis of perinephric abscess or an empyema There is leukocytosis Jaundice is very rare and ascites exceptional

The *prognosis* is very grave all Duvau s [8] forty cases terminated fatally The occurrence of secondary infections as in tuberculosis is the factor determining the gravity of the outlook for then iodides fail to exert a beneficial effect

The *diagnosis* depends on the recognition of the fungus in the pus This may be easy when the characteristic granules visible to the naked eye are discharged but in other cases many examinations may be necessary before it is

found and a diagnosis from other forms of hepatic or perihepatic suppuration established I have seen actinomycosis in a man deeply scarred from syphilis in whom iodides failed absolutely Opie[1 4] has described botryomycosis of the liver a condition due to an organism resembling staphylococcus pyogenes aureus

Treatment — Iodides in large doses, as much as 4 drams (16 gms) or more daily should be given, and in cases without pyogenic infection may have a remarkable effect but failures certainly occur, and Keynes[184] has emphasized this pointing out that the surrounding fibrosis may prevent the advent of the iodide Hence benefit has resulted from scraping the cavity and the local application of iodoform or iodin solution, from the combined effects of X rays and iodides from an autogenous vaccine, and from arsenic Kellock considered the intravenous injection of arsphenamin much more effective than iodides Copper salts have been employed both internally and locally, but their effect is not very encouraging Autogenous vaccines have often been tried (Colebrook[16], Keynes), but the results are not very striking

Lymphadenoma of the Liver

Synonyms — Hodgkin s disease lymphomatosis granulomatosa lympho granulomatosis (see Vol IV Chap I) In the late stages when the disease has generalized, the liver is invaded in about half of the cases, but not quite so frequently as the spleen

Clinical Picture — The hepatic enlargement is usually slight but the liver may reach down to the level of the umbilicus Symmers[18 a] reported a case in which the liver was enormously and, except for the spleen and abdominal lymphatic glands exclusively affected When the liver is much involved there is generally recurrent fever of the Pel Ebstein type, and in such cases it may be necessary to eliminate the fever of hepatic syphilis by the Wassermann reaction and of hepatic suppuration by a leukocyte count From pressure of enlarged portal glands on the bile ducts there may be obstructive jaundice recurrent jaundice may coincide with periodic waves of fever and glandular enlargement In rare instances ascites may occur and may even be chylous or pseudo chylous

In cases of fever with a swinging temperature and considerable hepat enlargement with but little or no implication of the superficial lymphatic glands, the clinical resemblance to hepatic abscess may be very close, but in the latter a leukocytosis may be expected, whereas in lymphadenoma there is no characteristic blood change

The prognosis is extremely grave Intravenous injections of arsphenamin are occasionally followed by temporary improvement X ray exposures are useless and possibly harmful

Hydatid Cysts of the Liver

The liver is more often the site of hydatid cysts than all the rest of the body put together, among Davies Thomas's 1897 cases the liver was affected in 57 per cent and among Devé's[186] 2 727 cases in 75 per cent the lungs coming next with 8½ per cent

Hydatid cysts in the liver may be single and without any contained daughter cysts this holds good in 90 per cent of the cases in children according to Devé who considers that reproduction is due to stimulation or injury of the cyst On the other hand it is not uncommon to find two or three distinct cysts crowded with daughter cysts in the same liver Devé[186] refers to livers containing 51 and 60 such cysts Exogenous formation of daughter cysts which project from the outside of the mother cyst though common in animals is rare in man and it has been thought that what has been regarded as exogenous formation is really projection of pseudopodial like processes of the original cyst with subsequent constriction of the pedicle However produced hydatid disease is in rare instances found permeating the liver along the portal spaces Any part of the liver may contain a cyst but the right lobe is naturally from its large size most frequently invaded The cyst is usually embedded in the substance of the organ but occasionally it is pedunculated and may then imitate the gall bladder the embryo may travel via the cystic veins to the gall bladder and develop primarily in its walls (Chauffard[187]) The size of the cysts varies the largest recorded contained forty liters (H B Robinson[18]) From destruction of a large part of the right lobe the remainder of the liver may undergo compensatory hypertrophy so that the left lobe becomes as large as the right Most exceptionally this hyperplasia has been known to pass into primary carcinoma of this rare sequence there are about six cases on record Hydatid cysts may as a coincidence be associated with cirrhotic or syphilitic change in the liver, with secondary malignant disease or with calculi in the gall bladder

Clinical Picture of Hydatid Cyst of the Liver

The existence of a cyst is often latent and only discovered accidentally or attention is first directed to the abdomen by its prominence and increasing size The general health is good and there is no loss of weight or vigor and the freedom from symptoms is in marked contrast to the hepatic enlargement A large cyst may cause a sense of weight or dragging but in uncomplicated cases especially in children pain is usually absent perihepatitis over the cyst omental adhesions epiploitis and the pressure exerted on the intercostal nerves by a cyst deeply embedded at the back of the right lobe may cause it From the irritation of a large cyst there may be pain referred through the sensory phrenic to the right shoulder or there may be pleurisy at the right base Spasm of the

bile ducts and colic possibly may be due to the toxic action of the hydatid fluid or to direct pressure of the cyst on the bile ducts, in which event there should be jaundice Pressure symptoms are rare probably from the slow growth of the cyst, but upward pressure on the thorax, especially when the abdomen is otherwise distended e g from pregnancy, may cause dyspnea, and pressure on the alimentary canal may be responsible for dyspepsia and constipation Asthma has been ascribed to the toxic influence of a hydatid (Renon[169])

Physical signs vary with the position of the cyst which when palpable is smooth elastic tense, regular and free from tenderness and so distinguishable from gummas new growth, and abscess Pain, usually stated to be rare, according to Quenu[190] occurs in more than half the cases, and there may be attacks of colic not explained by rupture of a cyst into the bile ducts Several cysts on the surface of the organ may obscure the diagnosis A cyst projecting from the anterior surface of the liver should be easily distinguished from an abscess or fibrous tumor (desmoid) in the rectus muscle

The hypochondrium may be visibly prominent, and by percussing the outstretched fingers of one hand the hydatid thrill may be but is often not, obtained When the cyst projects from the lower border of the liver a distended gall bladder may be exactly simulated, and the diagnosis must be made from other abdominal cysts such as peripancreatic and retroperitoneal A cyst in the left lobe may displace the heart upwards When embedded in the back of the right lobe and covered by liver substance a cyst may suggest massive carcinoma of the liver, but it is not tender or painful, constitutional symptoms are absent and the X ray picture is different, amyloid disease may be eliminated by the absence of constitutional signs, albuminuria splenic enlargement and the history By increasing the upward dullness the cyst may suggest a pleuritic effusion but exact determination of the dullness and an X ray examination should help

From disturbance of the functional activity of the liver the urine may contain bile salts Jaundice due to pressure on the bile ducts occurred in 44, or 8 7 per cent, out of 502 collected cases (Quenu[190]) a large cyst, and more particularly a pendulous one has in rare instances pressed on the inferior vena cava and caused edema of the feet diminution in the urinary output and distention of the caval system of veins over the abdominal wall In rare instances ascites, either mechanical or inflammatory in origin occurs (Robin, Weil and Bith[191]), and pseudochylous ascites has been recorded (Cattaneo) Eosinophilia is inconstant and is probably due to absorption of hydatid fluid, but it does not appear to be related to the hydatid urticaria The blood may show a characteristic precipitin reaction or deviation of complement but though a positive result in these blood tests is valuable, no significance can be attached to a negative Patterson and Williams[19] have described a stable preparation of hydatids for the complement fixation test

Diagnosis

The diagnosis of an uncomplicated hydatid cyst depends on the presence of a large cystic tumor of the liver with absence of constitutional symptoms but its parasitic nature cannot be certainly determined until hooklets or the laminated membrane have been detected or a positive result of the deviation of the complement test is obtained Puncture with a trocar through the abdominal wall though tempting should not be performed as severe collapse, convulsions and urticaria may follow the escape of hydatid fluid The fluid from a living cyst is said not to be toxic, but it is known that the fluid from a dead one exerts an effect resembling that of mytilotoxin and before paracentesis it is impossible to say if a cyst be living or dead even with living hydatid fluid symptoms have been ascribed to anaphylaxis The differential diagnosis has incidentally been dealt with

Prognosis

The prognosis of an uncomplicated hydatid cyst depends largely on operation if the abdomen is opened and the cyst removed all should go well if operation be delayed it may shrivel up and not give rise to further trouble On the other hand the complications referred to below may occur and it is therefore wise to recommend operation when the condition is suspected on good grounds

Complications

Suppuration may occur in growing cysts or in those that have apparently undergone spontaneous cure and the infection may be the result of tapping or be conveyed from the blood stream for example in malignant endocarditis typhoid fever puerperal infection influenza (Chauffard[193]) or be due to infection of the bile ducts associated with gall stones and is common when a cyst ruptures into the bile ducts It is relatively less frequent in children than in adults Vegas and Cranwell found its incidence in adults to be 14 per cent and in children 6 per cent Streptococci staphylococci pneumococci and B coli have been isolated in pure or mixed culture the pus may be highly offensive and in rare instances gas may form in the cyst from the presence of B aerogenes capsulatus or other anaerobes A suppurating hydatid may rupture into the bile ducts or leak into the peritoneal cavity and set up general peritonitis a subphrenic abscess or a subphrenic pyopneumothorax When suppuration occurs in a cyst the daughter cysts need not share in the infection and other cysts in the liver may escape The symptoms are those of hepatic abscess Eosinophilia if present previously disappears

1 *Rupture into Peritoneum* — Rupture of a hydatid cyst may take place into the peritoneum According to Devé[194] this occurs in 14 per cent of

the adult cases and 7 per cent of the cases in childhood It may be gradual and take place into a localized pocket of the abdominal cavity closed off by adhesions and an abscess may then follow Sudden rupture into the general peritoneal cavity may be fatal from shock, or set up general peritonitis if the contents of the cyst be infected If the cyst be dead and the fluid turbid and toxic, severe collapse and even fatal syncope may follow In other cases rupture of a cyst gives rise to sudden pain, urticaria, eosinophilia, and ascites which may persist for some time In some cases of which Devé collected 68, the peritoneal effusion is bile stained although there is no general jaundice from communication of the ruptured cyst with a bile duct In these cases the peritoneum is lined with granulation tissue containing bilirubin crystals, the bilious effusion is prone to recur after tapping and does not interfere with secondary hydatid infection of the peritoneum This is especially likely to occur in the pelvis and great omentum and it probably takes about two years for the secondary cysts to develop so far as to cause symptoms When the cysts are quite small the peritoneum has much the same appearance as in pseudotuberculosis of the peritoneum, also described by Devé due to granulomas containin booklets and pieces of hydatid membrane surrounded by granulation tissues and giant cells

2 *Rupture into the pleura* —A clear in very rare instances, bile stained or purulent effusion may result, and the latter may rupture into the lung

3 *Rupture into the lung* through an adherent pleura or with the intermediate stage of an empyema in the latter event a pyopneumothorax may follow The rupture may be fatal from suffocation A bronchobiliary fistula with discharge of bile may result and the hydatid cyst may become gaseous

4 *Rupture into the pericardium* is rare and fatal

5 *Rupture into the inferior vena cava and hepatic veins* is also very rare and usually, in eight out of Devé s eleven cases, rapidly fatal from embolism of the pulmonary artery or impaction of cyst in the right side of the heart

6 *Rupture into the stomach or intestines* may occur, but a diagnosis made on the presence of hydatid skins in the feces is open to the fallacy that they may have come down the bile duct

7 *Rupture of a hydatid cyst into the bile ducts* is important and fairly frequent, Devé [195] has collected 168 cases and finds that it affects the sexes equally When the communication is small the hydatid fluid may escape out of the cyst the bile run in, and the cyst dry up, so that few if any symptoms occur When the communication is large enough to allow daughter cysts to enter the ducts obstruction, colic and often infective or suppurative cholangitis are set up and the clinical picture suggests gall stones, from which it can be distinguished mainly by the discovery of hydatid cysts in the feces or vomit This may be suspected if a tumor in the liver diminishes in size after an attack of biliary colic The condition of the gall bladder in 94 cases of hydatid obstruction of the ducts has been analyzed by Devé, the gall blad

der is enlarged in 57 per cent and in 67 per cent of the cases with obstruction of the common duct or of the cystic duct This contrasts with Courvoisier's law namely that in gall stones obstruction of the common duct the gall bladder is not enlarged Gall stones may form either in the ducts or in the gall bladder as the result of the rupture of a hydatid cyst into the biliary system and Devé finds that this association is twice as frequent in men as in women The infected and dilated intrahepatic ducts may leak and give rise to perihepatic or subphrenic abscess or to general peritonitis and a subphrenic abscess may open into the pleura or lung and then cause a bronchobiliary fistula The prognosis in suppurative cholangitis is of course extremely grave

The Treatment of Hydatid Disease of the Liver

Simple puncture injection of antiseptics into the cyst acupuncture and electrolysis all formerly recommended and sometimes successful are not so satisfactory as free exposure of the cyst and expert surgical treatment No drugs have any effect on the disease but Devé recommends that when laparotomy is performed on a case of rupture of a cyst the abdomen should be washed out with ether which has a parasiticidal action on the scolices Arce's [96] observations which do not correspond with Devé's gave encouraging results from deep X ray therapy which appears to kill the parasite and render large cysts safer for operation and allows small cysts to become obsolescent

Alveolar Hydatid

There has been considerable discussion on the identity or otherwise of the parasite with Echinococcus granulosus whether it is merely an exogenous form of the ordinary parasite (Virchow) or a distinct species Echinococcus multilocularis The geographical distribution and anatomical characters are quite different in the two diseases Alveolar hydatid is met with in Russia South Germany Switzerland and Austria About four cases have been seen in the Jura in France (Martin and Tisserand [197]) a few imported cases have been recorded in America and it is unknown in Great Britain I have never seen a specimen The liver is enlarged and contains an encapsuled collection of irregular cavities some containing gelatinous cysts other caseous purulent or bile stained debris the whole resembling a colloid carcinoma or actinomycosis

The disease runs a chronic course with gradual onset of hepatic pain the liver enlarges and feels hard the spleen is almost always enlarged and jaundice usually present Diagnosis is very difficult and can be made almost only by microscopical examination of tissue removed at laparotomy with the detection of scolices The prognosis is bad unless excision the only method of efficient treatment be undertaken early

Fatty Liver

Under this heading it is convenient to include the two pathological processes of fatty infiltration or storage and fatty degeneration, the essential difference between them is that in the first the liver cell is not permanently damaged whereas it is in the second In fatty infiltration the liver is large with round edges pale and solid The liver cells at the periphery of the lobules are usually first affected though in pregnancy the cells in the central zone of the lobule may show the most fat Excessive fatty accumulation is seen in obesity, in over feeding in conditions of deficient oxidation, and in the later months of pregnancy

Fatty degeneration may but does not always, give rise to a flabby brittle state of the liver The cells in the central zone of the liver are usually most affected by the changes which, however, may be universal in the lobule and consist in a granular degeneration of the protoplasm with small particles of fat and chromatolysis of the nucleus Fatty degeneration is due to the action of various poisons such as alcohol chloroform iodoform, arsenic, antimony, mineral acids, bacterial toxins especially those of tuberculosis, and those active in gastrointestinal affections It may be pointed out that mild chloroform poisoning causes fatty degeneration but more intense poisoning produces necrosis In many instances conditions favoring both fatty infiltration and degeneration are present at the same time thus in tuberculosis of the lungs which is so commonly associated with a fatty liver, deficient oxygenation and toxemia are produced It has been shown that the extreme fatty change in experimental phosphorus and phloridzin poisoning is due to the transport of fat from other parts of the body and not to the local formation of fat from degeneration of the protoplasm of the liver cells It has therefore been thought that the damaged liver cell is unable to resist the deposit of fat which it cannot utilize, the fat being an index rather than the direct result of cell degeneration (Christian[198]), and that the term degenerative fatty infiltration is preferable (Herxheimer and W Hall[199])

The fatty liver is uniformly affected, smooth and usually much enlarged I have seen a liver weighing ten pounds (4 5 kilos) as the result of extreme alcoholism In some cases of degeneration it is small and flabby, but it is commonly firm though friable The specific gravity is diminished so that the organ may float in water

Clinical Picture of Fatty Liver

Clinically a fatty liver is usually subordinate to the conditions, such as tuberculosis, alcoholism, pernicious anemia cyclical vomiting, and delayed chloroform poisoning with which it is associated It is often latent, especially in obesity from the thickness of the abdominal walls and the relative softness of

the organ during life It is a painless smooth enlargement and is not accompanied by splenic enlargement or any special symptoms The blood pressure is low and the heart sounds often weak and distant

Prognosis

A patient with a fatty liver bears acute disease injuries and operations badly Injury to the hepatic region possibly may cause fat embolism in the lungs In a child with enlargement of the liver possibly fatty the administration of chloroform should be avoided on account of the risk of delayed chloroform poisoning It has been shown experimentally that previous starvation and a fatty diet render the liver extremely susceptible to the effects of chloroform poisoning and that a diet rich in sugar and carbohydrates the subcutaneous or intramuscular injection of epinephrin and the oral administration of quinin render the liver resistant to injury from chloroform (Davis and Whipple [90]) These observations may have a practical bearing on the prophylaxis of delayed chloroform poisoning

Diagnosis

In an alcoholic person a painless enlarged liver may be purely fatty or mixed cirrhotic and fatty and in the absence of any irregularity which would point to cirrhosis the diagnosis is difficult and mainly turns on the relative hardness the firm condition being in favor of cirrhosis In leukemia the spleen would almost certainly be enlarged and a blood count would settle any question

Treatment

The t eatment is that of the causal or associated conditions such as alcoholism obesity acidosis Experimental observations how that repair of the damage done to the hepatic cells by chloroform is accomplished most rapidly on a carbohydrate diet and that fats are valueless for this purpose (Davis Hall and Whipple [91])

AMYLOID DISEASE OF THE LIVER

In amyloid disease the liver is not so frequently attacked as the spleen and kidneys among 795 cases of lardaceous or amyloid disease the spleen was af f cted in 585 the kidneys in 539 and the liver in 387 The main causes of amyloido is are prolonged suppuration and syphilis even without suppuration but as prolonged suppuration has now become much less frequent syphilis is responsible for a higher percentage of the ca es than in the past It is occasionally seen in the liver in association with leukemia lymphadenoma pure actinomyco is malaria chronic infective arthritis and in rheumatic fever (Beattie [0]) Local amyloid change may occur in the liver around a gumma an

abscess or a suppurating hydatid Usually the change occurs slowly after prolonged suppuration, but it has been seen one month after the onset of osteomyelitis

The liver is uniformly enlarged and has been known to weigh fourteen pounds (6 4 kilos) It is smooth painless, free from tenderness, firm can be cut into slices thinner than in any other condition, retains its mouldings and from its enlargement the left lobe may show a fossa for the spleen it recalls His anatomical model of the organ The specific gravity is increased from the normal 1 055 to 1 080 It is anemic and has a rubbery feel but is less resistant to the knife than a cirrhotic liver The lobules are well marked out There is not any fibrosis as a result of the amyloid and other changes The middle coats of the small branches of the hepatic artery may also show the change but the liver cells are never amyloid The lymphatic glands in the portal fissure are enlarged

Clinically the liver is uniformly enlarged and smooth, but neither tender nor painful When combined with gummatous change it may be rough and nodular There are no symptoms directly due to the liver, such as jaundice Ascites, when present is usually the outcome of some complication or part of the general edema due to amyloid disease of the kidneys It is rare for the liver to be solely affected by the lardaceous change, and accordingly the patient usually shows splenic enlargement albuminuria dropsy, a low blood pressure, and diarrhea

Diagnosis — From other painless infiltrations, such as fatty and leukemic a history or evidence of a cause such as a positive Wassermann reaction is of value in the diagnosis In fatty liver the spleen is not enlarged leukemia can be recognized or ruled out by a blood count A large cirrhotic liver may be accompanied by an enlarged spleen and unless the surface of the liver be irregular may imitate amyloid disease evidence of past suppuration or syphilis is of course in favor of amyloid disease A deeply seated hydatid cyst is not accompanied by the deterioration of health and other signs of amyloidosis

Prognosis — The size of the liver is an index of the extent of the general disease and of the damage to other important organs, the kidneys and intestines The liver may get smaller under treatment

Treatment — The first essential is to remove the cause, suppuration or syphilis, by efficient measures It is doubtful if apart from such treatment, drugs exert any special influence on the morbid process but tonics, good food, and attention to the general health are important

Leukemic Infiltration of the Liver

The liver is usually enlarged in leukemia or leukocythemia it often weighs five or six pounds (2 3 to 2 7 kilos) and has been known to reach thirteen pounds (6 kilos) For a further description of leukemia see Vol II, Chap XVII

Cysts of the Liver

The following varieties of cysts may be found in the liver (1) Parasitic cysts hydatids (2) Cysts due to biliary obstruction from continued obstruc tion the intrahepatic ducts may be widely and fairly uniformly dilated and the contents may be quite thick tarry bile when the gall bladder is healthy and con centrates the bile or colorless white bile when the gall bladder is unable to perform this function the anatomical condition is comparable to a hydro nephrosis and has been termed hydrohepatosis (Rous and McMaster [9]) But sometimes the dilatation is more or less local North s case of a cyst con taining five pints (2 500 cc) of coffee colored fluid was associated with a calcu lus impacted in the common bile duct and except in this particular re embled the rare simple cysts of the liver (see below) In rare instances minute reten tion cysts are present in cirrhosis (3) Exceptionally multiple adenomas of the intrahepatic ducts form small cysts (4) Simple cysts are usually single or present in small numbers Constantine and Duboucher [4] consider these cysts as having the same origin as cystic disease As a rule the cysts are small and without clinical interest Jones [9] collected 61 operation cases and Zahn [08] collected 13 cases with ciliated epithelium A single cyst not parasitic or due to change in an adenoma of the bile ducts may contain many pints of fluid in Bayer s [9] and Winckler s cases 13 pints (6 5 liters) and in Aldous s 12 (6 liters) They are probably due to biliary retention though when large the bile may disappear and the fluid be clear Hemorrhage or sec ondary rupture of a bile duct may take place into these large cysts Fair sized cysts have been reported in infants without cystic disease of the liver (Durante [08] Elting and Shaw [9]) In rare instances the cysts have been pedunculated Like the simple cysts of the common bile duct females provide the vast majority of the cases out of 56 cases 44 were females (Jones [05]) The clinical symptoms and treatment are those of hydatid cysts from which they can be distinguished only by examination of their contents Jaundice has been seen in some in tances (Doran [10] Munk [11]) Extensive hemorrhage into or rupture of a cyst has given rise to very severe symptoms (5) Pseu tocysts due to softening down of carcinomatous or sarcomatous nodules usu ally the contents are blood stained but occasionally they are clear

Cystic Disease of the Liver

The liver is occupied by numerous cysts of various sizes The cases fall into two groups those in new born infants and tho e in adults though it is probable that the latter are survivals of the congenital condition Cases in infants are rarely reported in 1912 I collected 13 examples but the condition may easily be missed unless the liver is examined microscopically in two other cases

reported as cystic kidneys the livers showed a microscopic change (Leopold and Kunstler Royster) As in cystic kidneys the lesion may be hereditary and familial Cystic disease of the liver is nearly always accompanied by a similar but more advanced change in the kidneys, whereas cystic disease of the kidneys is common without the hepatic change In rare instances there are cysts in other organs the pancreas and the spleen It occurs three times more often in females, and usually the persons proved to have it are over fifty years of age

Morbid Anatomy

In infants the liver may be little if at all enlarged and few or no cysts visible to the naked eye, the organ appearing fibrotic from the sharp outlining of the portal spaces which resemble an oak leaf in shape (Bunting [1]) rather than cystic Microscopically there is fibrosis, mainly monolobular, containing dilated tubules lined by subcolumnar epithelium and resembling bile ducts, the hepatic cells may appear to be vacuolated In adults the liver may be greatly enlarged in McDonald s [13] case it weighed 14 pounds (6 4 kilos) The cysts are of various sizes encapsuled by fibrous tissue and may produce considerable deformity of the organ The contents of the cysts are usually clear, albuminous, and free from bile sometimes cholesterol, blood, leucin, and creatinin are present The larger bile ducts are normal The microscopical appearances are much the same, though older than those in the new born

Pathogeny

The pathogeny has been much discussed It has been described as a dysembryoma (Lettule and Verliac) Meyenburg [14] considers that the cysts are small bile ducts always connected with the liver cells but never with the larger bile ducts The most attractive explanation is that it is a congenital malformation due to irregular development into cysts of some of the hypoblastic cells forming the hepatic diverticulum, while the bile ducts proper develop in the ordinary manner (Still [15])

Clinical Features

Clinically apart from hepatic enlargement or the presence of cysts, which have been known to imitate an ovarian cystadenoma or a dilated gall bladder, symptoms pointing to the liver are wanting There appears to be always sufficient liver substance left to carry on its functions Jaundice and ascites are absent The symptoms are those of chronic renal disease from the megalocystic kidneys, such as uremia Clinically the kidneys may be regarded as hydronephrosis The combination of enlarged liver and kidneys with uremic symptoms should suggest the diagnosis

The treatment is that of chronic renal disease operative draining of the cystic liver should be avoided

Benign Tumors of the Liver

Solitary Adenoma

1 Solitary single or massive adenoma occurs as an encapsuled tumor of irregularly arranged liver cells without bile ducts and may or may not share in changes such as amyloid or chronic venous engorgement of the remainder of the liver which rarely shows cirrhosis Among Caminiti s twenty collected cases four showed cirrhosis A solitary adenoma may undergo necrosis and imitate a tuberculoma Possibly these single adenomas are inclusions of the hepatic rests or minute lobes sometimes present In rare instances more than one acinous adenoma is pre ent Deve describes a liver with four adenomas In some instances the liver cells may form tubules lined with cubical epithelium and containing plugs of bile Two forms have been described (1) benign adenoma or dysembryoma ( ) trabecular adenoma with a tendency to become malignant also called hepatoma Massive adenomas may be pedunculated and imitate a hydatid cyst in very rare instances rupture with intraperitoneal hemo rhage has occurred Primary carcinoma of the liver may be diagnosed and indeed may supervene (Cathala [8])

2 Adenoma derived from the mucous membrane of the bile ducts or from the mucous glands in the walls of the larger intrahepatic ducts may be single or multiple out of Gordinier and Sawyer s [9] 19 collected cases 15 were single and 4 multiple The single adenoma may become cystic and reach a large size as in Shattuck s case of a cyst containing a gallon (4 liters) of clear fluid microscopical examination of the cyst wall may be necessary to distingui h it from a simple cyst of the liver These cy tic adenomas of which Leppmann collected nine may simulate malignant disea e or hydatid of the liver or an ovarian cystadenoma Multiple adenomas of the bile ducts also commonly sho v cy tic change in Watzold s case there were forty adenomas with various degrees of dilatation The adenomas are usually encapsuled and there i often accompanying cirrhosis in Brigidi s case the liver was cirrhotic and weighed six pounds (2 8 kilos)

3 Adenomas due to included adrenal rests have in rare cases been de scribed (de Vecchi Schmorl) Doubt has been thrown by Stoerk and by Wilson and Willis on the adrenal origin of so called Grawitz tumors or renal hyper nephromas and also on the genuineness of hepatic hypernephromas by Glynn

Clinical symptoms are exceptional Flemming described an hepatic hy pernephroma which cau ed jaundice by compre sing the bile duct but it is not stated if a necropsy was made to eliminate the pos ibility that this was a

reported as cystic kidneys the livers showed a microscopic change (Leopold and Kunstler, Royster) As in cystic kidneys the lesion may be hereditary and familial Cystic disease of the liver is nearly always accompanied by a similar but more advanced change in the kidneys, whereas cystic disease of the kidneys is common without the hepatic change In rare instances there are cysts in other organs the pancreas and the spleen It occurs three times more often in females, and usually the persons proved to have it are over fifty years of age

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pressure on the bile ducts has induced jaundice and in few instances includ ing Hammer s case of an infant aged one week intraperitoneal hemorrhage has occurred A hemangioma in the left lobe of the liver obstructed the cardiac orifice of the stomach (Wakeley [31])

Prognosis in the cases which present clinical signs is apparently favorable if excision be undertaken

Other innocent tumors are very rare A lymphangioma which was pedun culated and so regarded as an ovarian cyst is on record Myxomas have been occasionally described in the past but some doubt as to benign nature may be entertained Some reputed fibromas, like those in the kidney (hamartoma fibrocanaliculare) have been recorded around the bile ducts A detached ap pendix epiploica may become embedded on the surface of the liver but a true lipoma is unknown Embryomas are very rare after rupture of an ovarian embryoma a secondary implantation cyst may occur on the surface of the liver

MALIGNANT DISEASE OF THE LIVER

This subject will be considered under the usual divisions of primary and sec ondary but as secondary malignant disease is so much commoner this will be dealt with first and in greater detail than primary malignant disease of the liver

SECONDARY MALIGNANT DISEASE OF THE LIVER

Secondary malignant disease of the liver is much commoner not only than the primary form but than innocent tumors hydatid cysts and gummas The liver contains secondary growths in 50 per cent of persons dying with ma lignant disease and is the organ most often occupied by metastases Secondary growths are from 20 to 40 times commoner than primary growths of the liver Of the secondary growths 77 to 91 per cent are carcinomatous The rarity of secondary sarcoma in the liver depends on the comparative infrequency of sarcoma generally and in the alimentary canal in particular

Sex — Females are rather more often attacked Hale White estimated the ratio as 4 3

Age — The patients are usually over forty and females on an average are attacked earlier in life than males Carcinoma of the liver secondary to the colon has been reported in a girl aged twelve years (Zuppinger [3]) and a boy aged thirteen (Ruczynski) The average age of patients with secondary sar coma is lower than in carcinoma The primary growth responsible for second ary metastases in the liver is most frequently in the stomach then in the colon esophagus pancreas gall bladder uterus and mammae Secondary growths in the liver are found in from 30 to 40 per cent of all cases of gastric car cinoma The carcinoma may spread directly up the lesser omentum into the

metastasis Saalmann [4] recorded an hepatic hypernephroma in association with von Recklinghausen's disease They have been successfully treated by partial hepatectomy (G G Turner [5])

Multiple Adenomas of the Liver

Multiple areas of hyperplasia of the liver cells are seen in very different conditions which however all have one factor in common, namely destruction of the liver cells as this destruction is also often followed by cirrhosis, the two results are often, though far from always associated In rare instances chronic venous engorgement is associated with multiple small areas of hyperplastic liver cells without encapsulation or cirrhosis, and a similar nodular hyperplasia may occur in malaria or in guinea pigs from experimental blastomycosis Usually multiple encapsuled hyperplasia is seen as a compensatory process in portal cirrhosis and to the naked eye is an exaggeration of the familiar hobnails they may closely resemble multiple nodules of malignant disease and may indeed become primary carcinoma with cirrhosis These tumors have therefore been regarded as a transitional stage to carcinoma, and the convenient noncommittal name hepatoma originally employed by Sabourin, has been revived The adenomas may undergo fatty change become hemorrhagic, or soften down and even discharge into the branches of the portal or hepatic veins Thrombosis may thus be induced or the portal thrombosis occasionally seen in cirrhosis may account for the degenerative changes in the adenomas As multiple adenomas are usually combined with cirrhosis the clinical features are those of that disease Large adenomas in subacute atrophy of the liver have led to laparotomy (Milne [6]) for an abdominal tumor

Angioma and Cavernoma of the Liver

Both these forms of a blood containing tumor occur in the liver According to Nicholson [7] angiomas are typical hamartomas, on the borderland between malformations and tumors They are rare in infancy and childhood (Veeder and Austin [8]), and though some may be congenital in origin, are usually found in elderly people Like other innocent tumors they may be multiple and in rare instances similar tumors have been found in the adrenals, ovaries and elsewhere (Shennan [9]) Usually the tumors are small and embedded under the capsule, but occasionally they are pedunculated These tumors may reach a large size in Major and Black s [10] case the liver weighed half the entire weight of the body They are usually encapsuled, and calcification of the capsule or even inside the angioma with the formation of phleboliths may occur

Clinically the large hemangiomas may imitate an hydatid cyst on account of the hepatic enlargement without grave constitutional symptoms Exceptionally

Sometimes from the rapid increase in the size of the liver and from the presence of ascites the patient although emaciating may retain his weight or even particularly *in the young gain weight Gain in weight may occur even without* ascites from liver enlargement (H A C) The enlarged right lobe may displace the diaphragm upwards and give rise to collapse of the base of the right lung and dullness on percussion Skiagraphy may be useful in showing the projecting nodules of growth in relation to the diaphragm The enlargement is les uniform than in cirrhosis and mainly of the right lobe In rare instances a venous hum can be heard over the liver Occasionally a mass of new growth pulsates from its free communication with blood vessels or conveys pulsation from the aorta or becomes soft and imitates an abscess Friction due to perihepatitis is not uncommon and is accompanied by pain There may be constant pain in the right hypochondrium or it may be felt in the back in the right shoulder or down the right arm The weight of the organ often causes discomfort which may be relieved by an appropriately fitted belt or bandage The spleen is very seldom enlarged but microscopic infiltration with carcinoma may cause splenomegaly (Kettle)

The abdomen may be much distended with enlargement of the subcutaneous veins mainly due to caval obstruction Small nodules may be felt around the line of the falciform ligament but these may be imitated by mall islands of fat Enlarged glands above the clavicles especially the left are due to metastases carried by the thoracic duct or the right lymphatic duct

Jaundice and ascites both occur fairly frequently but are rather accidental in that they depend on whether or not the bile ducts the portal vein and the peritoneum are directly involved by the growths Each of them occurs in about 50 per cent of the cases and both in about 20 per cent

Jaundice is rather more likely to occur early in the course of the disease when the primary growth is close to the liver in the pylorus or gall bladder and so likely to invade the bile ducts directly or by the pressure of an infiltrated gland to cause pressure indirectly Pressure of a gland on the common bile duct may cause jaundice with an enlarged gall bladder and so imitate carcinoma of the head of the pancreas Jaundice without absence of bile from the feces may be associated with obstruction of one hepatic duct or of an intrahepatic bile duct Jaundice may come on with vomiting and diarrhea as in catarrhal jaundice but persist The jaundice becomes progressively deeper and is commonly accompanied by pruritus which may be the patient s main complaint and cause serious insomnia

Ascites may be due to various factors pressure on the portal vein thrombosis peritonitis and perihepatitis set up by nodules of growth and widespread blocking of the intrahepatic blood vessels in angiosarcoma and melanoma The fluid may be clear bile stained mixed with blood from leakage from hemorrhagic growths chylous or chyliform In rare cases the ascitic fluid has been brown from melanin in cases of secondary melanoma of the liver

portal fissure, compressing the bile ducts on the way and so causing jaundice or a carcinoma of the cardiac end may infiltrate the left lobe, or embolic metastasis as in carcinoma of the colon may occur In 100 cases of carcinoma of the colon examined at St George s Hospital there were hepatic metastases in 34 but in many the nodules were quite small The primary growth may be extremely small and quite latent in cases with very large livers Sarcomatous and endotheliomatous growths in the liver are most frequently secondary to primary neoplasms in the adrenals mediastinum and to melanomas of the uveal tract and less often of the skin the former being sarcomatous, the latter generally epithelial in structure (D P Smith [35])

The liver may contain a few nodules only, but be enormously enlarged, 16 pounds (7 3 kilos) is not an uncommon weight Osler [6] mentioned a liver weighing 31[1] pounds (14 kilos) Christian [7] one of 33 pounds (15 kilos) and R Powell [38] one of 40 pounds (18 2 kilos) General jaundice may be associated with pressure on an intrahepatic bile duct but according to McMaster and Rous [39] it is due not to intrahepatic obstruction but to disordered function of the liver cells in many cases jaundice is due to pressure exerted on the bile ducts by enlarged glands in the portal fissure Pressure on the hepatic or sublobular veins may produce local chronic venous engorgement and pressure on the portal vein may cause thrombosis or ascites In rather rare instances secondary nodules on the surface of the liver grow directly into the abdominal wall Carcinoma may spread along the round ligament and give rise to a subcutaneous nodule near the umbilicus

Clinical Picture of Secondary Malignant Disease of Liver

The onset is usually gradual with loss of strength and weight Emaciation is much greater than in primary malignant disease as the patient may suffer both from the effects of the primary growth and from the hepatic metastases The wasting is often obvious in the face and temples and from the sunken eyes and the haggard aspect The cachexia is progressive Appetite fails and there may be disordered digestion even apart from the site of the primary growth A low form of fever is not uncommon and may be due to the rapid growth of the tumor or to a complication such as pyogenic infection of the growth or suppurative cholangitis

The enlargement of the liver is not always painful, the occurrence of pain depending mainly on the presence of perihepatitis a large mass of growth covered by liver tissue may be painless The irregular nodular surface of the liver is highly suggestive and the detection of a depression or umbilication on the surface of the projection is highly characteristic but this may be difficult to determine The enlargement is progressive and is mainly downwards so that the firm, hard, and perhaps irregular edge is felt below the umbilicus when the patient first comes under observation and eventually may almost fill the abdomen

mated The combination of a large liver ascites and considerable jaundice i sometimes seen in comparatively young and very alcoholic subjects with cirrhosis but generally this combination points to malignant disease in which the hepatic enlargement is less uniform and usually nodular Pain and emaciation are more prominent in new growth In Hanot s cirrhosis the large liver is smooth and there is splenomegaly which is exceptional in malignant di ease jaundice is constant but not completely obstructive the feces containing bile whereas in malignant disease jaundice if pre ent is progressive and the feces are usually colorless

Syphilitic disease and especially a large amyloid liver with gummatous projections may imitate malignant disease and luetic infection must always be considered Evidence of syphilis the Wassermann reaction and the effect of antisyphilitic treatment should be investigated In syphilis the spleen is often enlarged and when amyloidosis accompanies it albuminuria will probably be present

A deeply embedded hydatid cyst may produce enlargement suggesting massive carcinoma but the general health is usually unimpaired In rare ca es exogenous hydatid cysts may infiltrate the liver widely cau e jaundice suppuration and emaciation thus closely imitating malignant disease In alveolar hydatid this resemblance is also described but the spleen is usually enlarged and the course of the disease is slow

A rapidly growing soft sarcoma of the liver may fluctuate and the accompanying fever may produce the clinical picture of intrahepatic suppuration such as abscess or pylephlebitis Influenzal hepatitis sometimes imitates the early stage of malignant disease of the liver

The jaundice associated with a gall stone in the common bile duct is often regarded as due to malignant disease and as the gall bladder is not dilated the liver and not the head of the pancreas may be thought to be affected This view is particularly likely to be taken when a calculus passes into the common duct without the characteristic colic In these cases the jaundice and hepatic enlargement do not progressively increase they may indeed diminish There are periodic attacks of fever with pain and discomfort vomiting and transient increases in the jaundice

In rare ca es chronic venous engorgement of the liver without obvious cardiac disease imitates malignant disease The liver is enlarged and tender but smooth, and respiratory distress is an obvious feature

Other conditions with less claim to be regarded as malignant disease of the liver are a wandering liver leukemic infiltration of the liver a renal or supra renal tumor a Riedel s lobe due to a calculous gall bladder a tight laced constriction and fecal accumulation

The urine is usually high colored, uratic, free from albumin and sugar If jaundice be slight there may be absence of bile from the urine whereas with deep jaundice bile pigment and casts are present Urobilinogenuria is common except when bile is excluded from the intestine Creatin which is not present normally in the urine occurs and the amount is a measure of the malignancy of the growth (Mellanby[24]) In the melanotic tumors of the liver melanogen a colorless chromogen which yields melanin by oxidation with nitric acid or ferric chloride is usually present, and according to Eppinger[13], depends on extensive invasion of the liver which normally breaks down any melanin that reaches the circulation Melanuria may occur in the absence of a melanotic tumor (Peter[14] Haden and Orr[4]) Though clear when passed the urine becomes brown on standing Transient hematuria on one or two occasions may be the only indication that the primary growth is in the kidney The blood shows secondary anemia and often a moderate leukocytosis A positive Wassermann reaction has been reported without any other evidence of syphilis (Verdozzi and Urbani[15]) but this is exceptional in general experience Edema of the feet is very common in the later stages and in some instances peripheral neuritis occurs from hepatic inadequacy

The course and duration vary If the primary growth has been removed or remains quite latent life may be prolonged for a year or more But usually death occurs within six months of the time when the liver was first noticed to be enlarged and often it occurs much sooner F Taylor[4] however mentions a duration of three years and Christian[37] one of thirty five months Sometimes the liver progressively increases in size and the patient steadily goes down hill, in other cases a large liver remains stationary for a time and then suddenly a change occurs and death rapidly closes the scene The course of the disease is largely determined by the onset of hepatic inadequacy and the resulting toxemia, which in its turn depends on the amount of liver substance destroyed, on the presence of jaundice and on the urinary excretion

Diagnosis

Progressive nodular enlargement of the liver with loss of strength, emaciation, and evidence of a primary growth fully justifies a diagnosis But the existence and site of a primary growth cannot be determined during life in about half the cases and accordingly although the diagnosis of malignant disease of the liver is certain the question whether it be secondary or primary often remains open The special features of primary malignant disease have been mentioned already

The *differential diagnosis* must be made from a number of conditions causing enlargement of the liver especially when combined with jaundice and ascites In portal cirrhosis with ascites and jaundice it may be impossible to make a diagnosis until the abdomen is tapped and the size and state of the liver esti

Sex — Primary carcinoma is much commoner in males this is particularly so in primary carcinoma developing in a cirrhotic liver out of 58 collected cases 4 only were in females In primary sarcoma the sex incidence is not so definitely settled among 32 collected cases over 10 years of age 19 were females and 13 males

Age — Primary carcinoma usually occurs about the age of 50 years among Eggel s [49] 163 cases the average age of the males was 53 and of the females 52 years In 4 cases that I collected the average age of 29 males was 49 and of 13 females 42 years About 20 well authenticated cases in children are no record, but there are many more cases reported as such Castle [250] referred to 4 Primary sarcoma of which Jaffe [51] accepts 48 as genuine may occur at any age There are two groups those in early life and those in later life Foote collected 9 cases of hemangio endothelioma in infants which is malignant but not a typical angiosarcoma and does not give rise to metastases

Primary carcinoma may occur in the following forms (1) Massive a large white or yellowish tumor expanding the liver usually spheroidal celled derived from the polygonal liver cells There may be secondary growths in the organ According to Eggel [9] this accounts for 23 per cent of the cases (2) Multiple or nodular primary carcinoma resembles ordinary secondary carcinoma but without any primary growth In Eggel s [2 9] series this occurred in 64 per cent of the cases and he must have included the next group of cases (3) Primary carcinoma with cirrhosis or cirrhosis carcinomatosa has given rise to discussion as to the relation between the cirrhosis and the growth It seem most satisfactory to regard the cirrhosis as the primary change and the carcinoma as the outcome of the compensatory hyperplasia of the hepatic cells Fried [3] who endorses this view, shows that the stroma of the growth consists of capillaries, whereas in primary carcinoma arising from bile duct epithelium there is a secondary fibrosis According to Pirie [1 0] primary carcinoma relatively often supervenes in the natives of South Africa who have cirrhosis from schistosomiasis In 1922 M Stewart [54] collected six cases of primary carcinoma in hemochromatosis There are multiple tumors which may invade the portal or hepatic veins and so cause thrombosis Secondary growths may contain bile (4) Diffuse or infiltrating primary carcinoma is the rarest of Eggel s [49] forms occurring in 12 per cent of his series

The relative frequency of the origin of primary carcinoma from the liver cells and from bile duct epithelium (cholangioma) respectively has been variously estimated the general opinion is that most cases are derived from the hepatic cells Primary carcinoma derived from included adrenal rests have been described but Clynn [5] and Nicholson [6] consider that they really arise from liver cells Starr [51] and Harrigan [8] successfully removed hypernephromas of the falciform ligament Gall stones are very rarely associated with primary carcinoma of the liver Secondary growths occur in the liver in the adjacent lymph glands and sometimes in the lungs

Treatment

Treatment is mainly palliative and consists in the relief of pain by morphin which need not be withheld a suspensory belt may obviate discomfort and a feeling of dragging due to the weight of the organ Indigestion may be helped by hydrochloric acid which is indicated by the diminution of HCl in the gastric juice in malignant disease not only of the stomach but of other parts of the body and by the probability that in its absence secretin and therefore the pancreatic secretion are deficient Vomiting should be treated by bismuth morphin and dilute hydrocyanic acid Constipation should be prevented by salts and mild laxatives and colic flatulence by minute (1/20 gr, 0 003 gm) doses of calomel three times daily Abdominal massage should be avoided For itching, calcium salts by the mouth warm alkaline baths, dabbing the skin when the irritation begins with carbolic lotion one in sixty the hypodermic injection of pilocarpin atropin or morphin should be tried Diet should be determined by the patient s inclinations and alcoholic stimulants will usually be welcome Experimental observations do not lend any support to the view that increased diuresis from water by the mouth increases the excretion of bile pigment (Haessler Rous and Broun ') In all cases of the slightest doubt the condition should be treated as if it might be syphilis Operation can rarely be anticipated to do any good as the metastases are nearly always multiple

Primary Malignant Tumors of the Liver

Primary malignant tumors of the liver apart from those of the gall bladder and extrahepatic bile ducts are rare the ratio between primary and secondary malignant tumors of the liver has been estimated at 1 20 (Hale White) and 1 40 (Hansemann) This rarity is remarkable in the light of the great power of compensatory hyperplasia possessed by the liver

Primary Carcinoma

Primary carcinoma is much more frequent than primary sarcoma of the liver and moreover some reputed cases of primary sarcoma in very early life may be examples of congenital syphilis and the small group of reputed primary melanotic sarcomas are not free from the possibility that they were in reality secondary to a minute growth in the uveal tract There may be difficulty in deciding on the nature of the growth confusion may arise between endothelioma and carcinoma, and sarcoma and carcinoma have been described in the same liver (Saltykow) and the name carcinoma sarcomatodes has been given to such a tumor

caused nervous symptoms (Mosny and Moutier [81]) Splenic enlargement is therefore somewhat in favor of primary as against secondary new growth It has been thought that primary sarcoma runs a more rapid course than carcinoma (Pepere)

The diagnosis from other conditions and the treatment are much the same as in secondary malignant disease (vide p 417)

The prognosis is of course hopeless Operation has been performed in a number of cases Yeoman [6] collected nine excisions for primary carcinoma but the chance of cure is remote In a few instances the disease has disappeared either spontaneously (A P Gould) after influenza (Campbell [284]) or after injection of the patient s own ascitic fluid (Hodenpyl [6] Ewing [4]) but these are among the curiosities of medicine

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Primary Sarcoma

Primary sarcoma may occur as (1) A massive tumor corresponding to massive carcinoma This is the commonest form, accounting for 22 out of Pepere s [9] 45 cases The tumors may be very hemorrhagic and break down to form false cysts (2) Multiple or nodular primary sarcoma, resembling secondary metastases, making up 18 of Pepere's series (3) Diffuse or infiltrating form which must be distinguished from the liver of congenital syphilis (4) Primary sarcoma in a cirrhotic liver is very rare in 1924 Jaffe [1] collected 14 cases and also 3 of both primary sarcoma and carcinoma in a cirrhotic liver (5) Primary melanotic sarcoma has been reported in 11 cases but, as mentioned above, it is doubtful if the claim can be sustained

Chorion epithelioma

Chorion epithelioma has been described as a primary tumor, but though cells resembling syncytial cells are admitted doubt has been thrown on their origin Brault [60] calls them angioplastic sarcoma Vascular tumors, obviously malignant but of debatable nature — perithelioma, endothelioma, or angiosarcoma — occur and are sometimes given the non committal name of hepatoma an unfortunate and confusing title as it has also been applied to carcinoma with cirrhosis

Clinical Picture of Primary Malignant Disease of the Liver

The clinical picture of primary malignant disease of the liver presents a general resemblance to that of secondary growths and attention will here be directed to the points of difference Occasionally the involvement of the liver escapes detection and the disease is regarded as arteriosclerosis uremia or most exceptionally as general paralysis of the insane from the presence of secondary metastases in the brain As compared with secondary malignant growths the course is shorter the enlargement of the liver more rapid emaciation, ascites and jaundice less prominent, and fever more frequent Jaundice and ascites each occur in about 55 per cent of the cases Rupture of the splenic vein in carcinoma with cirrhosis has been recorded (Ogilvie [241]) Multiple nodules on the surface of the liver are rather in favor of secondary growth and of course evidence of a primary growth elsewhere for example carcinoma of the breast or rectum, is decisive Splenic enlargement occurred in 32 per cent of Eggel s [49] 163 cases and is often due to portal thrombosis which is usually seen in association with primary carcinoma with cirrhosis in rare instances there is widespread round celled infiltration of the liver and spleen resembling leukemia until the blood is examined in some of these cases meningeal metastases have

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CHAPTER VII

DISEASES OF THE GALLBLADDER AND BILE DUCTS

By ALBERT M. SNELL

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I DISEASES OF THE GALLBLADDER

Historical Foreword

It is possible to recognize three distinct periods in the medical history of disease of the gallbladder first the development of knowledge of the symptoms caused by gallstones and the pathologic conditions associated with them second a period devoted to the development of surgical measures of relief and finally the present era which has been concerned largely with the development of the experimental and clinical physiology of the biliary passages and the detection and treatment of the earlier stages of cholecystic and hepatic disease

The earlier history of our knowledge of disease of the gallbladder deserves but brief mention here, for a fuller account Wilkie s[1] chapter should be consulted The first authentic descriptions of stones in the bile passages is attributed by some to Gentilis de Foligno (1348) and by others to Marcellus Donatus who is said to have noted a stone in the ampulla of Vater In the writings of Antoninus de Benivinius (1592) there is also an account of the finding of gallstones but the first description of the symptoms produced by gallstones seems to have been that of Jean Fernel (1581) who attributed their formation to thickened bile and obstruction in the ducts Johann Kent

II DISEASES OF THE BILE DUCTS

During this same period an extraordinary amount of work dealing with the functional activities of the liver and biliary system some of which has been of immediate practical importance has come from the laboratories of physiologists The problem of the clinician is that of applying both these newly acquired facts and those gained by a half century of surgical experience to the diagnosis and treatment of the troubles of the patient before him He must concern himself particularly with the matter of differentiating those patients whose only help lies in radical treatment from those whose condition may be relieved by simpler measures It is to be hoped that the next advances in treatment will be in the application of physiologic principles to the management of earlier stages of cholecystic disease

ANATOMY

From the standpoint of structure and function the fundus and body of the gallbladder are designed to form an apparatus whose chief properties are those of concentration The infundibulum neck and the valvular cystic duct have predominantly motor and secretory properties The remaining portions of the extrahepatic bile passages with the exception of the distal portion which forms a sphincter are largely passive tubes This muscular end of the common bile duct first described by Oddi (1887)[2] is anatomically inconspicuous but of great physiologic importance It consists of a collection of oblique and longitudinal muscular bands in the intraduodenal portion of the common duct with an encircling band of muscle fibers at a somewhat lower level Recent studies of microscopic preparations (Halpert quoted by Mackey[3]) indicate that in some human subjects this sphincter is absent or virtually so

The finer structure of the gallbladder gives evidence of its functional properties The mucous surface which is obviously adapted for absorption consists of tall columnar epithelium thrown into deep rugæ Beneath this a fibromuscular coat consisting of transverse longitudinal and diagonal smooth muscle fibers is found the muscular layers being much more pronounced at the two ends of the organ and relatively sparse in the midportion In the infundibulum of the gallbladder the muscle fibers tend to form a circular arrangement which is carried on into the neck and the valves of Heister These latter structures consist of deep mucosal folds arranged in corkscrew like fashion the valves also contain some circular muscle fibers They have been thought to retard the free flow of bile in and out of the cystic duct thus maintaining the bile in the gallbladder in a somewhat uniform state For further details of anatomic structure the reader is referred to descriptions by Hendrickson[4] Brewer[5] Halpert[6] and Sweet[7] who have each reviewed the ana

man (1565) published the first illustrations of stones, Hildanus (1612) noted their lamellated structure and also credited his predecessor, Fabricius, with the operative removal of stones from the gallbladder of man, a procedure now believed to have been performed only on the cadaver Glisson and Sydenham each left a good clinical description of biliary colic and other symptoms of cholecystic disease Entmuller (1667) paved the way for modern radical surgical treatment by the statement that "There are no medicines which will dissolve gallstones and even when the cholelithiasis appears healed the stones soon recur and lead to death' Haller and Morgagni writing in the latter half of the eighteenth century, summarized the prevailing clinical knowledge of disease of the gallbladder indeed, the descriptions in De Sedibus et Causis Morborum were not greatly improved on until a century had passed

The second period that devoted to the development of methods of treatment begins with the work of Jean Petit (1743) who is credited with the first deliberately planned operation for removal of stones His attempts at surgical treatment were confined chiefly to cases in which external fistulas were present or in which a distended gallbladder was fixed to the abdominal wall There were no further surgical advances for a century, and even by the latter part of the nineteenth century little progress had been made in spite of many theoretical suggestions and a few bold ventures by Kocher Sims, Tait and others who performed cholecystostomy in occasional cases with varying degrees of success Cholecystectomy was first successfully performed by Langenbuch in 1882 by 1890 Courvoisier was able to report that he had himself performed the operation forty seven times The first successful operations on the common duct were also carried out during this period In the thirty years which followed surgical technic was perfected, and the indications for cholecystostomy and cholecystectomy became generally recognized

The increasing familiarity of the profession with surgical methods and the development of cholecystography as a ready means of laboratory diagnosis has made the last decade notable for the number of surgical procedures performed for every type and degree of disease of the gallbladder It is only natural that the great benefits derived from surgical treatment of advanced and neglected cholecystic disease should have led to attempts at correcting such conditions in their earlier stages and in fact this thought has to a certain extent dominated surgical practice in recent years This common practice of removing gallbladders for all sorts of digestive disturbance because cholecystographic examination or the results of duodenal drainage seem to indicate they are diseased has filled the period with numerous distressing lessons in the clinical physiology of the extrahepatic bile passages and it has also convinced observers that the gallbladder is not so frequently the sole cause of pain and digestive symptoms as had been supposed

Physiology

The subject of the physiology of the gallbladder does not lend itself readily to condensation and for details and bibliographic references the reader is referred to the extensive reviews by Mann[8] Ivy[9,10] and Newman[11] As one would expect from its embryonic origin the gallbladder manifests the general properties of the intestinal tract namely those of absorption secretion and motor activity

Concentration

The absorptive properties are of particular importance the gallbladder being by virtue of these properties as Ivy and Bergh[1] have said a reservoir of small volume and great capacity As Rous and McMaster[13] and Mann and Bollman[14] have shown conclusively the gallbladder has a pronounced concentrating effect on bile The former investigators showed that the hepatic bile was concentrated from four to ten times by the absorption of water and of such inorganic salts as sodium chloride and sodium bicarbonate and of other readily diffusible substances The bile becomes slightly acid in the process the p^H of normal liver bile ranging from 7 to 8 5 whereas that of gallbladder bile varies from 5 5 to 7 Calcium probably is absorbed from the gallbladder but because of the greater removal of water this element tends to become concentrated in the bile Under normal conditions the absorption of bile pigment and bile salts is slight and concentration of these substances is the rule[15] The data on absorption of cholesterol are difficult of evaluation the normal mucosa may absorb a relatively small amount[15] whereas the inflamed or abnormally functioning mucosa may under some circumstances actually excrete cholesterol into the bile Numerous diffusible chemicals and dyes may be absorbed it is important to note that the absorption of those used in cholecystography is not sufficiently great to account for the disappearance of the shadow of the gallbladder

In pathologic conditions such as acute inflammation empyema and hydrops the concentrating activity of the gallbladder is lost in whole or in part In milder grades of cholecystic disease there may be only a slight decrease in the rate of absorption in the severely damaged gallbladder absorption may cease entirely and fluid may flow into the lumen carrying with it numerous substances which are ordinarily absorbed In some types of cholecystic disease the concentrating properties of the gallbladder may be increased Caylor and Bollman[16] have shown that this is the rule in papillomatous gallbladders and in those with hypertrophied villi In general as Ravdin and his colleagues[17,18] have shown the concentrations of calcium and bile salts fall with increasing

tomy of the bile passages the two last mentioned investigators considering the subject with reference to physiologic activity

The external relations of the gallbladder and its vascular and lymphatic connections require brief mention The organ itself lies in a fossa on the inferior surface of the liver in close relation to the second portion of the duodenum and to the hepatic flexure of the colon The only free peritoneal surface is on its inferior aspect there is sufficient mesentery to allow of motion in only about 10 per cent of cases Angulation of the gallbladder on the common duct is almost a universal finding and is not necessarily referable to an unusual motility The anatomic relations of the gallbladder are such that perforation when it occurs is most frequently into the duodenum and least frequently into the small bowel or colon free perforation into the peritoneal cavity being relatively rare

The arterial supply of the gallbladder is furnished largely by the cystic artery Anomalies in the course of this vessel are common, accessory cystic arteries are found occasionally as well as large vessels which pass directly to the gallbladder from the liver The lymphatic drainage is chiefly into nodes along the cystic and common ducts and also into a group of nodes near the head of the pancreas a large node at the angular junction of the neck of the gallbladder with the cystic duct being a well known surgical landmark. There are free connections with the lymphatic vessels in the capsule of the liver a fact which is emphasized by the frequent finding of local areas of hepatitis around a diseased gallbladder As with other hollow abdominal viscera there is a double innervation the principal nervous connections being those derived from the vagus and the splanchnic sympathetic nerves

The comparative anatomy of the gallbladder is of some importance, if only because it has been invoked to throw some light on the function of the organ One of the difficulties in explaining cholecystic function arises from the fact that many species have no gallbladder While uniformly present in carnivora and primates it is not found in any living structure lower than fishes and there are at least eighteen species of fish which have no gallbladder It is uniformly absent in the horse rat and pocket gopher and present in the cow and in such closely related species as the mouse and the thirty two striped gopher The capacity of the extrahepatic bile ducts appears to be no greater in animals without a gallbladder than in those with one in some of the former however the liver has been shown to secrete a more concentrated bile, thus compensating for the lack of facilities for storage In all species, which do not have a gallbladder the sphincter of the common duct is inconspicuous, and bile flows in a continuous trickle contrasting to the intermittent flow which is found in animals provided with a gallbladder

been demonstrated[22] however that there is no increase in the bilirubin cholesterol or iodine content of hepatic duct bile during the disappearance of the cholecystographic shadow and therefore by exclusion it may be inferred that the cystic duct is the normal route of evacuation

All the available evidence indicates that the gallbladder fills in an inter digestive phase and that its contents are discharged into the duodenum by way of the cystic and common ducts after a meal In connection with this cycle of filling and emptying the sphincteric mechanism of the ampulla of Vater is considered as part of the functional unit which regulates cholecystic evacuation This sphincter is in contraction during the fasting state and can when contracted resist a pressure at least two or three times as great as that which the gallbladder is capable of exerting namely o to 30 cm of bile. This state of sphincteric contraction is necessary to allow the gallbladder to fill, and conversely the sphincter must relax during the period in which the gallbladder is evacuating its concentrated bile To explain this mechanism one must still invoke the Doyon Meltzer[23] concept of reciprocal activity for which adequate physiologic proof is now available It has not yet been decided whether this mechanism is an active or a passive one but there are many facts which clearly connect the activities of the sphincter with those of the gallbladder After cholecystectomy the sphincter becomes incompetent and bile dribbles into the bowel exactly as it does in species of animals who have no gallbladder Later it regains its tone and may be responsible in part for the dilatation of the extrahepatic bile ducts which eventually follows

The mechanisms by which contraction of the gallbladder is brought about have only recently been satisfactorily explained on the basis of hormonal activity For years it has been held that such accessory factors as respiratory movements postural changes the milking action of the duodenum peristalsis in the common duct the elastic recoil of the gallbladder and so forth play a part in evacuation of the gallbladder It is now generally agreed that these are unimportant and that there is no constant correlation between the motor activities of the gallbladder and those of the intestinal tract except during the passage of food into the duodenum at which time a hormonal stimulus to cholecystic evacuation is produced *Emptying of the organ apparently is not due, at least to any considerable extent to nervous stimuli* although these may play a part in certain pathologic conditions Vagal stimulation produces a *general spastic contraction of the gallbladder and sphincter and cessation of* the flow of bile while sympathetic splanchnic stimulation causes relaxation of the gallbladder and contraction of the sphincter of Oddi It is obvious that these mechanisms do not explain the usual process of evacuation of the gall bladder but rather interference with its normal emptying

The hormone which brings about normal contraction of the gallbladder

damage to the mucosa whereas the concentrations of chloride and bicarbonate increase These workers have also noted that the cholesterol content of bile may under some circumstances as yet not clearly defined be roughly parallel to its content of bile salt while under other conditions the concentration of cholesterol may be increased with a reduced content of bile salt There are curious abnormalities of the concentrating function in respect to calcium salts, which may be found in high concentrations in the walls of some pathologic gallbladders and in the bile There is no evidence of significant absorption from the common and hepatic bile ducts they may dilute the bile with mucoid secretion but otherwise do not alter it in any way

Secretion

The mucosa of the gallbladder forms a mucoid secretion, the character of which is due chiefly to nucleoalbumin The normal output of this secretion probably does not exceed 20 c c in twenty four hours, but in the presence of acute irritation of the wall of the gallbladder there is an out pouring of secretion in a manner suggestive of that which appears during some forms of catharsis The question of whether or not significant quantities of cholesterol are contained in this secretion under normal conditions has been settled in the negative, but under pathologic conditions such as hydrops the wall of the gallbladder may elaborate a fluid containing cholesterol White bile, which probably represents a true pathologic biliary hypersecretion, contains small amounts of cholesterol and calcium

Motor Activity

The ability of the gallbladder to contract and to empty itself by way of the cystic duct which ability has been denied in the past has now been established by numerous physiologic studies [19] Evidence to this effect has been obtained by surgical and roentgenologic means and by chemical analysis of the duodenal contents The direct evidence is particularly striking Kalk [9] has visualized contraction of the gallbladder by endoscopy after an injection of pituitrin numerous observers have noted a rearrangement of shadows of gallstones into a column of twos in serial films taken after the administration of tetraiodophthalein and Matsuo [1] has observed contraction of the gallbladder directly at laparotomy

It can also be shown that the disappearance of the shadow of the gallbladder after administration of tetraiodophthalein is due to evacuation by way of the cystic duct This has been contested and the process has been explained on the basis of absorption through the wall of the gallbladder Recently it has

The general functions of the gallbladder may be summarized by saying that it acts as a storage reservoir for the concentration of bile and that it correlates the secretory activities of the liver with those of the gastrointestinal tract during the various phases of digestive activity. Ivy[9] is impressed with its pressure regulatory function which acts as a factor of safety to maintain the normal structure and physiologic activity of the biliary passages. Certainly its activity as a storage reservoir delays the development of jaundice in biliary obstruction and in this way spares the liver to a considerable extent. The known functions of the sphincteric mechanism are those of assisting in the filling of the gallbladder and preventing regurgitation of duodenal contents; no doubt there are others as yet undiscovered.

As many physiologists have stated there are a number of general problems yet to be solved. An explanation of the differences existing between the various species still is lacking. A more complete understanding of the choledochoduodenal junction, its physiology and its relation to motor disturbances of the biliary passages possibly would explain many obscure clinical syndromes. Finally the relation of disturbances of the motor, absorptive and secretory functions of the gallbladder to the production of cholecystitis and cholelithiasis still is an unexplored field and one which may hold the solution of many pressing clinical problems.

Pathology

Anatomic Abnormalities

Numerous anomalies of the gallbladder and bile ducts have been reported in both man and animals and these variations have received much attention from comparative anatomists and from surgeons. Congenital absence of the gallbladder has been noted[30] and Schachner[31] has collected instances of double, bilobed, bifid and intrahepatic gallbladders. A floating gallbladder with a long mesentery is observed not infrequently, a condition which may lead to torsion and to necrosis from interference with the blood supply[32]. Diverticula from both the neck and body have been described. In transposition of the viscera the gallbladder has been found in the left lobe of the liver, and occasionally a gallbladder has been noted on the left side even in the absence of situs transversus. Duplication of the cystic duct, anomalies of its insertion into the common duct and abnormal forms of entry of the common and pancreatic ducts into the duodenum are not uncommon. These anomalies of the ducts and of the vascular supply of the gallbladder have been reviewed by Eisendrath[33] and by Flint[34]. Kehr[35] also has listed a long series of anomalies and abnormalities. Schachner[31] noted that in about 18 per cent. of cases anomalies of the gallbladder and ducts were multiple. The chief importance

cholecystokinin can be extracted from the duodenal mucosa [1], and when injected intravenously, it causes a prolonged contraction of the gallbladder with evacuation of its contents. The physiologic activity of this hormone has been fully verified by crossed circulation and transplantation experiments. In the intact subject production of the hormone is brought about by the introduction of acids and fats into the duodenum, egg yolk and cream being the most effective stimulants, proteins ranking next in activity and carbohydrates having little or no effect. Cholecystokinin is a more powerful excitant of cholecystic contraction than any known drug; its action is not abolished by atropine, and it appears to be independent of any ordinary nervous influences.

For obvious reasons a great deal of attention has been given to the study of both the normal and abnormal motor activities of the gallbladder. The concept that biliary stasis is responsible in part for the production of cholecystic disease in general and of stones in particular has of itself stimulated much study of this matter. Ivy [9] has reviewed the literature bearing on this problem in detail, and a full discussion will not be attempted here. In the intact human subject it is probable that the gallbladder does not completely renew its contents after every meal or indeed during a single day, dietary factors being the controlling element exactly as is the case with the colon. The process of evacuation in normal subjects is fairly well understood owing largely to the efforts of Boyden and his associates[26, 27], who studied the matter by means of serial roentgenograms of the dye filled gallbladder after a fat meal. Boyden [8] has noted three types of evacuation, each of them involving contraction of the gallbladder and relaxation of the sphincter in various time sequences. In the type most commonly observed contraction and evacuation start with simultaneous relaxation of the sphincter and the gallbladder empties almost completely in about two hours. In another type there is simultaneous relaxation of the gallbladder and of the sphincter with a temporary delay in emptying; in a third the initial phase of emptying is followed by refilling with prolongation of the evacuation time.

Abnormalities in cholecystic evacuation and their relation to cholecystic disease are as yet only imperfectly understood. In the presence of experimental cholecystitis evacuation is considerably delayed or may be entirely absent, the power of the gallbladder to contract may however be regained as inflammation subsides. Westphal [9] mentions various abnormal types of evacuation, chief of which are (1) a hypermotile gallbladder with rapid emptying, (2) a hypertonic contraction of the gallbladder against a spastic sphincter, and (3) relaxation or atony of the gallbladder with spasm of the sphincter. The probable effect of these abnormal contractions in producing symptoms or in laying the foundation of cholecystic disease will be considered in a later paragraph.

[1] Vol. III 936

Dietary and metabolic factors have not as yet been assigned their final places in the etiology of this condition The relation of disturbed cholesterol metabolism to cholecystic disease in general has been vigorously debated and still is in a controversial stage part of the difficulty arising from the diversity of experimental methods used and the introduction of extraneous factors It appears that there may be definite types of both calculous and non-calculous cholecystic disease which are predominantly due to faulty cholesterol metabolism Even in the absence of visible inflammatory change under certain conditions the mucosa of the gallbladder may become loaded with cholesterol or actual cholesterin stones may form Granted that the bile cholesterol may be increased by dietary or other means and that such changes may result in the deposition of cholesterol in the mucosa or precipitation of cholesterol within the lumen of the gallbladder we are still confronted with the problem of how these two factors operate to produce gallstones or cholesterol deposits in the mucosa Since bile salts have something to do with keeping cholesterol in solution it has been assumed that hepatic activity in respect to the production of these salts may also have something to do with the matter complete proof of this hypothesis has not however been provided

The element of infection in the production of disease of the biliary tract in general looms very large and there are many investigators who look upon all benign forms of cholecystic disease as essentially of an infectious nature Moynihan's[41] dictum that every gallstone was the sarcophagus of one or more organisms is an example of this school of thought Undoubtedly systemic infectious diseases focal infections and inflammatory disease of the alimentary tract all leave their imprint on the liver and gallbladder a previous attack of typhoid fever for example may figure in from 5 to 25 per cent of cases of disease of the gallbladder Just how frequently other and less serious infectious diseases in early life lay the groundwork for the chronically diseased gallbladder of later years cannot be determined but the incidence probably is considerable

The relation of infection or functional abnormalities of the hepatic parenchyma to cholecystitis probably is more important than has been generally supposed The almost universal finding of hepatitis and cholangeitis of greater or lesser degree in association with an infected gallbladder has been remarked by many surgical observers and has been thought to have some special significance There is still no conclusive evidence to indicate whether this phenomenon is a cause or an effect but its importance must be admitted. It has also been argued that repeated mild episodes of cholecystic infection with partial recovery of structure and function may be responsible for some of the changes in the wall of the gallbladder now looked upon as essentially metabolic in nature or they may lead to aberrations of function in respect

of these anomalies is the difficulty which they add to surgical procedures on the biliary passages Anomalous arteries or abnormalities in the course of the cystic artery have been thought to interfere with the emptying of the gall bladder thus leading to biliary stasis and infection[36]

General Factors in the Production of Cholecystic Disease

It is the usual practice to consider the etiology of cholecystitis and cholelithiasis under separate headings, a distinction which seems rather artificial, since the relation of previous inflammatory processes to the formation of stone or at least the association of the two conditions is well established There are certain types of cholecystic disease which are almost certainly due to metabolic disturbances others appear to be entirely of an infectious nature by far the greater number however represent a combination of these two factors together with some physiologic perversion of the activity of the gallbladder as a concentrating organ.

There are certain general observations on the predisposing causes of cholecystic disease which appear to be of some importance The incidence of the disease appears to be greatest in highly civilized ' countries with a large urban population such as Germany England and the United States and lowest in Japan Russia Korea Central Africa and in the tropics In other words cholecystic disease is less frequent in countries with a large agricultural population where hard work and a vegetarian diet are the rule These differences in incidence may be more apparent than real, and possibly they are to be attributed to better general facilities for diagnosis in the countries first mentioned Many of the earlier students of the subject have mentioned a sedentary life, tight lacing heavy eating obesity constipation and visceroptosis as predisposing factors but such factors are probably of minor importance

Cholecystitis and cholelithiasis are about three times as commonly found in females as in males This universal predominancy of cholecystic disease of all types in females is not easily explained Pregnancy has been invoked as a factor, the gallbladder presumably suffering as a consequence of hypercholesterolemia and biliary stasis The importance of the latter factor is not clear, although Fogelson[37] noted that failure of visualization of the gallbladder by cholecystography is common in pregnancy, and Mann and Higgins[38] have noted delayed evacuation in pregnant experimental animals Gross[39] statistics indicate that pregnancy is probably not a significant factor Hosoi and Alvarez[40] have gathered statistics which show that even in early life cholecystic disease is much more common among females than males, they also pointed out that typhoidal cholecystitis is twice as common among young girls as boys With advancing age the sex ratio is greatly altered, and in patients more than sixty five years of age the predominance of females is reduced to a 2 to 1 ratio

which on intravenous injection into animals produced infection of the bile or gallbladder in 75 per cent of the animals studied Bacillus coli commonly was found in association with streptococci and frequently it was grown from the bile or wall of the gallbladder in cases of empyema Rehfuss and Nelson[47] obtained practically the same results and Wilkie's[48] results also are similar In addition the last named investigator reported 86 per cent of positive cultures from the sentinel lymph node that drains the cystic duct and gallbladder Branch[49] found organisms in only 12 per cent of chronically diseased gall bladders however he noted positive cultures in 75 per cent of cases of acute cholecystitis as did Nickel and Judd[9]

In addition to the common invaders a very imposing list of organisms has been isolated from the gallbladder This includes among others bacillus pyocyaneus bacillus influenzæ bacillus aerogenes capsulatus[1, 50] bacillus enteritidis brucella abortus[32] and vibrio choleræ The pneumococcus occasionally may produce a very severe and acute cholecystic infection

Cholecystitis

Pathogenesis

The pathologic picture of cholecystitis is an extremely variable one and represents all degrees of damage from mild catarrhal changes in the mucosa to suppuration or gangrene To a large degree the extent and character of the pathologic condition depends on the presence or absence of stones in the gallbladder and the virulence of infecting organisms A previous attack of inflammation renders subsequent inflammatory changes easier to produce and microorganisms lying latent in the wall of the gallbladder may lead to severe inflammatory lesions especially if the cystic duct becomes temporarily obstructed Gallstones of course render the organ particularly liable to acute inflammation the same statement applies to other foreign bodies Any other mechanical factors which produce partial biliary obstruction or stasis also favor the development of infection in the wall of the gallbladder The pathologic picture may be complicated further by antecedent or associated infection of the liver and bile passages the hepatic lesions may resolve while those in the gallbladder remain active or there may be primary involvement of the gallbladder later extending to the liver

The gallbladder itself can become infected in one of five ways (1) by direct local extension from an inflamed viscus (2) by ascending infection by way of the common and cystic ducts (3) by way of the portal vein to the liver and thence through the hepatic lymphatics to the gallbladder (4) by blood borne infection conveyed through the hepatic artery or (5) through its

to evacuation of the gallbladder, in turn leading to biliary stasis or perversions of the concentrating activity of the gallbladder However, it has been shown that the gallbladder may function normally, at least in respect to cholecystographic dyes after an episode of inflammation and residual damage to its mucosa For this and other obvious reasons the full scope of infection in the production of disease of the biliary tract is difficult to evaluate properly, it seems probable, however, that those who regard all cholecystic disease as having an infectious origin can make out a somewhat better case than those who incline to metabolic and functional theories of etiology

Finally, the idea as expressed by Schmieden and Rohde[4] that 'biliary stasis' is responsible for cholecystic disease may be mentioned As Newman[11] has pointed out the term has been used loosely, and its exact limitations have never been defined It does seem well established that certain functional disturbances in the evacuation of the gallbladder exist[43] That spasm of the sphincter of the common duct or of the circular muscle fibers in the neck of the gallbladder may cause temporary retention of bile in the gallbladder is difficult to dispute that it ever leads to complete and permanent failure of evacuation of the gallbladder is doubtful If it could be proved that prolonged and complete stasis of bile in the gallbladder did exist because of disturbances of motor function the fact would be of considerable importance, since experimental ligation of the cystic duct can of itself produce definite changes or even actual cholecystitis, in the normal gallbladder of the dog[44] The whole subject has been critically reviewed by Newman[11], who concluded that the significance of functional stasis in the production of cholecystic disease probably has been overestimated

BACTERIOLOGY

It is possible to refer to only a few of the numerous bacteriologic studies of the diseased gallbladder and its contents Judd and his collaborators[4, 46] examined a series of pathologic gallbladders removed at operation and found only 14 per cent with positive bile cultures They noted that the thick, greenish black bile occurring in cholecystitis is not necessarily infected, whereas thin, 'grainy blood tinged bile usually yields positive cultures In their series a considerably higher incidence of positive cultures 68 per cent, was obtained in cases of acute cholecystitis In cases of chronic cholecystitis with stones cultures of gallstones were positive in 31 per cent, and cultures from the wall of the gallbladder were positive in 39 per cent In one series of 100 cases bacillus typhosus and paratyphosus never were found, although there was an antecedent history of typhoid fever in 21 per cent of the cases The organism most commonly encountered was a green producing streptococcus

ization of bacteria has produced cholecystitis in experimental animals by the intravenous injection of streptococci from tonsils and teeth and he has assumed that cholecystitis is essentially a blood borne infection While his results are not universally accepted the fact remains that one of the commonest organisms recovered from the gallbladder on culture is a short chain streptococcus the common intestinal organisms being in the minority and being possibly secondary invaders Wilkie[48] also concluded from his extensive bacteriologic studies that in a majority of cases cholecystitis is a blood borne streptococcic infection Rehfuss and Nelson[7] recently have reviewed a large series of bacteriologically studied gallbladders and reached the conclusion that distant foci are responsible for infections of the gallbladder in a high percentage of cases these foci occurring chiefly in the oral cavity and in the alimentary tract Burton[63] has made the interesting observation that in cases of subacute bacterial endocarditis cholecystitis is not uncommon and that the sex and age incidence under these conditions is not that usually observed He gave details of three such cases in which the lesions in the gallbladder resembled closely those described after the experimental intravenous inoculation of streptococci

The production of acute chemical cholecystitis by intravenous injection of Dakin s solution[64] raises the question of possible occurrence of toxic cholecystitis in the human subject It is probable that a number of chemical or bacterial toxins are capable of injuring the mucosa of the gallbladder and it seems reasonable to assume that under such conditions secondary infections might occur from organisms present in the bile or wall of the gallbladder

Acute Cholecystitis

While acute cholecystitis may occur in the course of acute infectious disease it is associated most frequently with antecedent chronic inflammatory change in the gallbladder which in turn is most often associated with the presence of stones In Baumgartner s[65] series of acute and subacute cases stones were found in 96 per cent In a series of 508 cases of acute cholecystitis reported by Judd and Phillips[66] nearly half the patients had suffered definite symptoms of cholecystic disease for various periods before the final attack which led to cholecystectomy Four hundred and eighty four of these patients had calculi in the gallbladder and forty three also had choledocholithiasis

Pathologic Changes

It has been observed repeatedly that in acute or subacute cholecystitis there is no constant correlation between the severity of clinical symptoms and the pathologic findings noted at operation the pathologic changes varying from

lymphatics and venous blood supply The first mode, that of direct local infection is decidedly rare although cases have been described in association with typhoid fever and similar involvement from penetrating duodenal ulcer However this mechanism cannot be a significant factor in the general production of cholecystic disease The second mode, that of an ascending "chologenous" infection must also be something of a rarity, the normal activity of the sphincter of Oddi being sufficient to prevent such an occurrence The duodenum ordinarily is sterile and the opportunities for direct bacterial contamination are not particularly large, especially if hydrochloric acid is present in the gastric contents However in the presence of active duodenitis it is conceivable that there may be some involvement of the common duct and Crain and Walsh[54] have shown that an experimentally produced chemical duodenitis delays evacuation of the gallbladder, thus favoring the development of infection Finally there is some experimental evidence to suggest that pancreatic juice can be diverted into the common duct under certain conditions and that it may set up a chemical type of cholecystitis[55], which may in turn tend to activate organisms already latent in the wall of the gallbladder

The third mode that of infection by way of the portal blood and hepatic lymphatics must be considerably more common The liver is one of the great bacterial filters of the body, and it normally supports a considerable bacterial flora chiefly of intestinal origin There is no reason why such organisms may not gain access to the gallbladder through its lymphatic connections. That this route may be important is shown by the very frequent association of local hepatitis with cholecystitis, many surgical authorities have stressed the clinical association of subacute cholecystitis, cholangeitis and hepatitis[56–60], and experimental proof of this route of infection is not lacking While it is agreed that a liver which has been loaded with organisms by experimental or other means may secrete infected bile which of course has free access to the gallbladder yet cholecystic infection is not ordinarily accompanied by the presence of organisms in the bile In fact organisms are much more likely to be confined to the wall of the gallbladder, a point which suggests direct extension by way of the lymphatics in the capsule of the liver Graham and his collaborators[6, 7] have made out a strong argument for this route of cholecystic infection for details and bibliographic references the reader is referred to their monograph The observations of Meyer and his associates[61] on experimental typhoidal inoculation also lend support to this theory, and it has also been championed by Moynihan[41] The principal question, which arises, is how frequently this is the route of selection for infection of the gallbladder, that it is a common one can hardly be questioned

Another source of infection is the arterial blood reaching the gallbladder by way of the cystic artery Rosenow[6] who has stressed the elective local

be remarkably complete the mucosa in particular exhibiting extraordinary powers of regeneration. However chronic infection may remain in the deeper structures and pericholecystitis with local adhesions is a very common development Hydrops or chronic empyema may date from an acute attack but probably only if the cystic duct is occluded by the inflammatory process or by stone The liver frequently suffers in one of three ways most commonly by local or general hepatitis or cholangeitis infrequently by abscess, which is usually confined to the gallbladder fossa very rarely by pylephlebitis with multiple abscesses Associated pancreatitis chiefly of the chronic or asymptomatic type is encountered frequently and in occasional cases there may be hemorrhagic pancreatitis with fat necrosis

Symptoms of Acute Cholecystitis

The clinical picture of acute infectious cholecystitis is a variable one in the absence of stones the process may be extremely mild and may pass unrecognized No doubt many minor episodes of supposed indigestion or biliousness represent a mild catarrhal inflammation of the gallbladder When noncalculous acute cholecystitis is of a degree which permits clinical recognition the onset usually is gradual with nausea anorexia chilly sensations and occasionally slight fever The pain which usually begins as an indefinite aching in the epigastrium and right upper quadrant of the abdomen may become increasingly severe It is often of a continuous aching character and rarely reaches the proportions of a true biliary colic There may be radiation to the back especially to the lower angle of the scapula Pain referred to the neck or shoulder usually is indicative of local peritonitis with diaphragmatic involvement

On *physical examination* the liver may be found somewhat enlarged and tenderness is often noted even in the left lobe Tenderness on pressure in the right costovertebral angle and along the lower ribs is not uncommon and there may be cutaneous hyperesthesia along the right costal margin Spasm of the right rectus muscle usually interferes with satisfactory palpation of the gallbladder but occasionally it may be distended sufficiently to be palpable Visible slight jaundice is noted occasionally and not infrequently one sees cases in which the cholecystitis appears to be only part of a general infection of the biliary tract Graham[68] believed that jaundice in acute cholecystitis is often due to a distended Hartman s pouch pressing on the common duct There are undoubtedly cases in which the process in the gallbladder subsides and the principal brunt of the infection is borne by the liver Minor degrees of elevation of the serum bilirubin with direct van den Bergh reaction have been noted repeatedly and the excretory function of the liver may be otherwise impaired as shown by retention of bromsulphalein even in the absence of bilirubinemia[9] In general

mild inflammatory ones with edema and injection of the walls to frank suppuration involving the wall of the gallbladder and its contents, or even necrosis and gangrene

Acute catarrhal cholecystitis reveals a minimal amount of change in the macroscopic appearance of the gallbladder On microscopic examination leukocytic or lymphocytic infiltration of the mucous membrane may be noted. In more advanced and subacute forms the mucosa has a velvety appearance, there may be edema of the wall of the gallbladder and minute hemorrhagic lesions in the submucous coat As the process progresses, the serous coat shows engorgement of vessels and may be dulled by the deposition of fibrin, local adhesions pericholecystitis, are commonly found The lymph nodes along the cystic duct are enlarged In more advanced cases the mucous membrane becomes increasingly congested and edematous, and there may be epithelial desquamation The cystic duct may become blocked either by stones or by inflammatory edema Occasionally the gallbladder is found to be distended but more often it gives this appearance because of the engorgement and thickening of its walls At a somewhat later stage there may be definite formation of an exudate within the gallbladder, the bile may be thinned bloody or frankly serous, containing mucous flakes and epithelial debris If the process progresses the contents of the gallbladder may be replaced by a purulent exudate ordinarily, however, the so-called empyema of the gallbladder does not represent an acute process so much as it does a slow accumulation of pus in a chronically infected organ In the most severe grades of acute cholecystitis described as "phlegmonous" the mucous membrane becomes shaggy and necrotic and often may be separated from the muscular coat by layers of pus At this stage ulceration of the mucosa may occur and the ulcerated areas may either granulate or progress to form areas of gangrene, which penetrate through the wall of the gallbladder These areas of impending perforation usually are seen near the fundus and appear to represent interference with the blood supply possibly caused by the pressure of stones Actual gangrene of the entire wall is rare it may result from torsion of the gallbladder or occlusion of the cystic artery In general, the most extreme grades of acute cholecystitis are to be attributed to three factors, to highly virulent infecting organisms to a cystic duct blocked by a stone, or to interference with the blood supply

The normal course of acute cholecystitis is subsidence without perforation the incidence of perforation being about 12 per cent. in Judd and Phillips'[87] series Perforation when it does occur tends to be localized to the region of the gallbladder, the incidence of general peritonitis being low Stones may ulcerate through the wall forming fistulas into adjacent viscera particularly the duodenum Curiously enough healing after acute cholecystitis may

clinical signs by which the presence of suppuration within the gallbladder can be determined the general and local symptoms may be more severe than in non suppurative varieties and the fever and leukocyte counts higher signs of local peritonitis may appear Occasionally marked toxemia and evidence of general infection complicate the picture An indefinite tender mass is often palpated in the region of the gallbladder In general one suspects the presence of suppuration in patients with acute cholecystitis whose symptoms persist and become more severe *Gangrene of the gallbladder* is due as a rule to infection by a highly virulent organism in the presence of occlusion of the cystic duct by stone the latter being an almost invariable finding Such occlusion may be produced by torsion in the rare instances in which the gall bladder has a mesentery sufficient to allow such a condition to occur The clinical symptoms are not characteristic and are seldom sufficient to justify a pre-operative diagnosis[74]

In most cases acute cholecystitis whether with or without stones, tends to subside spontaneously within seven to ten days Definite improvement usually is noted within the first forty-eight hours but if such improvement does not appear one is justified in suspecting the development of complications or of an inflammatory process progressing to suppuration The important complications local abscess peritonitis fistulas pylephlebitis have been mentioned in an earlier paragraph

As has been stated *perforation* is relatively rare and when it does occur is not necessarily due to areas of gangrene in the wall of the gallbladder Leakage of bile from the acutely inflamed gallbladder by way of Luschka s crypts or free perforation is an extremely serious affair as McWilliams[75] statistics show The free escape of sterile bile into the peritoneal cavity may be associated with fatal peritonitis[6] Pancreatitis if sufficiently severe to produce symptoms may manifest itself by a shift of pain into the left upper abdominal quadrant and by increasing lumbar pain If actual pancreatic necrosis ensues shock and board like rigidity of the abdomen will be noted Hepatic involvement which may be transient and slight or may be of considerable degree has been mentioned already The development of chronic empyema or even of abscess in the bed of the gallbladder may be attended by remarkably few symptoms and as Judd and Waldron[74] have shown this is also true of gangrene Severe pain continued fever leukocytosis marked upper abdominal tenderness and muscular spasm should arouse suspicion that such developments are taking place

Chronic Noncalculous Cholecystic Disease

There are certain reasons for considering chronic noncalculous disease of the gallbladder separately the first being that such disorders presumably

leukocyte counts are not particularly reliable guides to diagnosis, although a slight leukocytosis of 10,000 to 15,000 cells per cubic millimeter is the usual finding

The *acute cholecystitis* that occurs during the course of *typhoid fever* deserves special comment It is probable that in a majority of cases of typhoid fever the bile passages contain living bacilli, but clinical cholecystitis occurs in something less than one per cent of cases Young adults are affected most frequently The disease process is of course masked by the symptoms of typhoid fever and in most of the cases on record the condition was not detected until an extensive suppurative cholecystitis was present Perforation occurs with considerably greater frequency than in the ordinary varieties of cholecystitis and for obvious reasons the mortality of surgical intervention is high Thomas[70] Ashhurst[71] and Reid and Montgomery[72] have reported cases with perforation and have summarized the literature Following typhoid fever there may be latent typhoidal cholecystitis which may continue for years without symptoms it is from this group of individuals that typhoid carriers are segregated Hurst[36], Thomas[70] and others have cited cases in which typhoid bacilli have been isolated from the gallbladder and from gallstones more than twenty years after the original disease

In *acute cholecystitis associated with stones* the symptoms are more severe than in the noncalculous forms and they may come on with alarming suddenness Vomiting abdominal distention chills, fever and violent upper abdominal pain are common initial symptoms The pain, which usually is attributed to blocking of the cystic duct by stone, resembles biliary colic except that it is more likely to be continuous and severe and morphine usually is necessary to secure even partial relief Radiation of pain toward the back and into the thorax is the rule and such pain is accentuated by the slightest movement on the part of the patient or even by the effects of respiration Muscular spasm upper abdominal tenderness and rigidity indicate the spread of the process to the peritoneal surface The gallbladder may be distended to a considerable size and can be palpated in approximately 20 per cent of cases, some observers set this figure somewhat higher As in the noncalculous forms of cholecystitis there may be evidence of hepatic involvement and jaundice is not uncommon It should be understood that jaundice appearing under these conditions does not necessarily imply the presence of a calculus in the common duct Hartman[73] noted that about 30 per cent of patients with calculous cholecystitis proved surgically gave a history of jaundice or presented themselves while visibly icteric in spite of the fact that in each instance no stones were demonstrated in the common duct at the time of operation

The acute and subacute *suppurative forms of cholecystitis* are almost invariably associated with stones but they may occur when the cystic or common duct is occluded by neoplasm or by parasites There are no reliable

some instances epithelial proliferation and the formation of small cysts is noted, *cholecystitis cystica*.

The serous coat usually is opaque and there may be adhesions to the adjacent viscera. Lymph nodes in the vicinity, particularly the cystic node, usually are enlarged. The bile itself may be dark and tarry, but in some instances it is thin and watery. In either of the foregoing types of bile one may find sandy material, fibrin or desquamated epithelium. If for any reason the cystic duct is occluded, the gallbladder becomes distended either with clear colorless material, mucocele, or with frank pus, empyema. A patchy type of inflammatory process with local ulceration, *chronic ulcerative cholecystitis*, also is described. In such cases fistulas may form even in the absence of stones.

Strawberry Gallbladder

Among the curious forms of cholecystic disease the strawberry gallbladder deserves particular mention because of its probable metabolic origin. There are some investigators who do not feel that it represents a disease process and who claim that it produces no symptoms except when associated with stones or secondary infection. It is an extremely common form of cholecystic disease, Mentzer[77] finding it alone in 28 per cent of cases in his series and in about an equal number of cases in association with cholesterin stones or cholesterin-laden papillomas. The condition was first described by Moynihan[78] and later and more fully by MacCarty and his associates.[80, 81] The descriptive term *cholesterosis* was suggested by Mentzer.[82] The yellow deposits which stud the mucosa of the gallbladder give the condition its characteristic appearance and its name. Boyd[83] has shown that these deposits consist of cholesterol esters.

The presence of cholesterosis of this type has repeatedly been advanced to support the claim that certain types of cholecystic disease may be of purely metabolic origin. Blaisdell and Chandler[84] claimed to have reproduced the condition by feeding cholesterol and they attributed the deposits to absorption by the mucosa of cholesterol from bile. Elman and Graham[85] thought that it was related to an infectious process of low grade and that under such conditions the gallbladder excreted cholesterol. Illingworth[86] produced the condition experimentally by feeding large amounts of cholesterol in the presence of mild bacterial infection of the gallbladder. Wilkie and Doubilet[87] suggest that when the cholesterol concentration of bile is greater than that of the blood, cholesterol passes through the mucosa toward the blood stream, whereas if the blood cholesterol is the higher, the migration will be in the opposite direction. In spite of these studies the pathogenesis of the condition is not yet clear and

represent the earliest stages of chronic cholecystic disease, which may lead to the formation of stones and the more serious types of pathologic changes, and the second being the established fact that the outlook for complete symptomatic improvement after cholecystectomy is definitely less favorable in this group of cases than in those in which stones are present. A very high incidence of minor inflammatory and supposedly "metabolic" changes in the gallbladder has been noted by many students of the subject, and in any large series of necropsies at least 60 to 75 per cent of gallbladders examined are the site of some type of pathologic change.[7] The problem of the physician is to sort out from this large and heterogeneous group of cases those in which patients will be benefited by surgical procedures.

Judd[78] has emphasized the point that we do not actually know what constitutes "chronic cholecystitis" either from a clinical or pathologic standpoint. As Mackey[3] has said, "cholecystitis without stone seems to belong to a region on the borderline between functional and organic disease." The unfortunate feature is that, as is the case in acute cholecystitis, there is no constant relation between the severity of the symptoms and the pathologic changes encountered. In general, two fairly well defined types of disease of the gallbladder are encountered by the surgeon in this group of cases: (1) *chronic catarrhal or chronic fibrous cholecystitis* and (2) *cholesterosis* or *strawberry gallbladder*. Finally, there is a well recognized group of patients who present definite clinical symptoms of cholecystic disease but who have little obvious pathologic change in the gallbladder. Presumably this is the group of cases in which motor disturbances of the gallbladder or ducts are responsible for the production of symptoms, which cases have been described as examples of "*biliary dyskinesia*" or in earlier writings as "*stasis gallbladders*." The symptoms of the three groups are more or less identical, and, unfortunately, physical, laboratory, or roentgenologic examination will not clearly differentiate one from the other. The symptomatology will be dealt with in a later paragraph.

Chronic Catarrhal or Fibrous Cholecystitis

The pathways by which bacteria may reach the gallbladder have been mentioned already, and the evidence cited seems to indicate that the usual route of infection is through the blood stream. The pathologic changes produced in the gallbladder are variable, the usual sequence of events being the development of a chronic inflammatory process in the wall of the gallbladder with more or less subsequent fibrosis. Cases of atrophic or sclerosing cholecystitis represent the extreme degree to which such a process may progress. Ordinarily, the mucous membrane may show hypertrophic or hyperplastic change; less commonly it may be atrophic or even completely destroyed. In

are described as intermittent and relief obtained by taking food may be a feature Nausea and anorexia extrasystolic arrhythmias and spastic constipation are said to be present The gallbladder on roentgenologic examination is said to empty slowly the stomach is hypertonic and on duodenal intubation and the instillation of oil there is a long latent period before bile flows In atonic distention which is mentioned as an affection of older and thinner individuals the pain is described as being of a heavy continuous aching type which does not radiate and is aggravated by taking food Gastric acidity is reduced the stomach is of the atonic type on roentgenologic examination and empties slowly Cholecystography is said to show a long thin type of gall bladder with a shadow of reduced density and a prolonged period of evacuation On duodenal intubation there is a flow of bile only after long periods

While these syndromes are rather nebulous it must be admitted that one occasionally sees patients who fit the general description given by the previously mentioned investigators and who appear to have some motor disturbance of both the biliary and digestive tracts There is some physiologic evidence in regard to the motor function of the gallbladder which seems to indicate a basis for these syndromes of dysfunction further clinical experience may serve to establish them as definite entities but for the present the matter must be held sub judice

General Symptoms of Noncalculous Cholecystic Disease

There are no rules by which noncalculous chronic inflammatory cholecystitis or cholesterosis can be differentiated from each other or from the chronic calculous varieties of cholecystitis Pain of approximately equal severity is a predominant symptom in noncalculous cholecystitis and cholesterosis and reflex motor disturbances of the digestive tract usually are conspicuous accompaniments If the process is predominantly an infectious one occasionally it may be identified by low grades of fever leukocytosis and local tenderness Cholesterosis is encountered with greater frequency in obese individuals and has been said to be associated with hypercholesterolemia The clinical associations of the stasis gallbladder or of biliary dyskinesia as has been indicated are as yet distressingly vague

The symptoms which have been thought to be associated with both types of chronic noncalculous cholecystic disease are variable in the extreme and cover almost the whole range of human ailments The most curious fact about many of these symptoms is that they are relieved in whole or in part in a fair percentage of cases by removal of the offending organ without particular respect to the pathologic changes encountered The results are as Graham and Mackey[89] and Judd and Priestley[90] have shown fairly good if colic has been

it is not certain whether the cholesterol in the wall of the gallbladder represents a product of secretion or of absorption Elman and Taussig[83] have produced evidence to show that the gallbladder may excrete cholesterol, whereas Boyd[8] believed that the mucosa may absorb it The true nature of the process is obscure but it appears to represent a perversion of cholesterol metabolism quite possibly brought about by the milder grades of cholecystitis Mackey[3] believed that cholesterosis is not of itself a pathologic or symptom producing condition However it is not infrequently associated with papillomas, which may be laden with cholesterin, and in an even larger percentage of cases the strawberry gallbladder will contain almost pure cholesterin stones

'*Stasis Gallbladder*' or "*Biliary Dyskinesia*'

The third group of cases, those in which more or less typical cholecystic dyspepsia and pain in the right upper abdominal quadrant are present in spite of the grossly normal appearance of the gallbladder at operation, is very confusing and only imperfectly understood It is a well recognized fact that all of the symptoms of cholecystic disease including those closely resembling colic, may be present without much visible evidence of either infection or cholesterosis, yet removal of the gallbladder not infrequently will relieve the presenting symptoms There are two explanations of this phenomenon (1) that associated hepatitis and cholangeitis are responsible for the symptoms, a theory which certainly does not apply to all cases, and (2) that the symptoms may be produced by abnormalities of evacuation of the gallbladder such as stasis or contraction against a spastic sphincter with secondary or reflex disturbances in the digestive tract The actual pain is not difficult to explain Ivy and Sandblom[43] have shown that contraction of the gallbladder against a spastic sphincter of Oddi will produce severe pain, which can be relieved by the introduction of magnesium sulphate or olive oil into the duodenum to relax the sphincter Various types of abnormal evacuation as described by Westphal[9] have been mentioned previously (1) vagal overactivity leading to rapid emptying of the gallbladder or to spasm of the sphincter with cessation of biliary flow and (2) sympathetic overactivity leading to relaxation of the gallbladder and spasm of the sphincter also with cessation of the flow of bile The symptoms and signs associated with these disorders of motility are as yet not clearly defined nor definitely accepted

The *symptoms ascribed to biliary dyskinesia* may deserve special consideration, there is a good discussion of them in Newman's[11] review Spastic distention is said to be commonest in obese women of the so-called vagotonic type the principal complaint is of mild colicky pain, radiating to the back and often occurring at night, or when the patient is fatigued The symptoms

matory disease of the upper respiratory passages has been emphasized by some observers Tenderness in the region of the gallbladder may be present but it is seldom marked except after acute exacerbations The gallbladder itself rarely can be felt a tender liver edge may be noted Laboratory methods cholecystography duodenal intubation and drainage will be discussed in a later paragraph

Rare Infectious Lesions of the Gallbladder

Chronic cholecystitis resulting from such specific infectious diseases as syphilis tuberculosis and actinomycosis is to be classed with the pathologic curiosities Syphilis of the gallbladder is apparently a particularly great rarity Actinomycotic involvement has been described[93] Tuberculosis apparently is more common Lazarus and Eisenberg[94] recently have described a case and cited nineteen others from the literature Four cases have been seen at the Mayo Clinic in one of these[95] tuberculous peritonitis followed cholecystectomy and in two others there was localized tuberculous peritonitis in the vicinity of the gallbladder Walters and Church[96] described a case in which cholecystectomy was performed without incident It is curious that in none of these cases was there evidence of tuberculosis outside the peritoneal cavity The usual symptoms are those of chronic cholecystitis with a tender tumor in the right hypochondrium *Echinococcus disease* which frequently attacks the liver may affect the gallbladder by extension the condition is referred to in the section on diseases of the bile ducts later on in this chapter Ascaris lumbricoides has been found in the gallbladder and in distomiasis the liver fluke has been found in a similar situation Endameba coli and endameba histolytica have also been found in a few cases (see Vol V Chapter XXXIII) and also organisms of doubtful pathogenicity such as giardia lamblia and various types of trichomonas but it is not clear that these parasites produce symptoms (see Vol V Chapt XLII)

Gallstones

Incidence

The earliest accounts of gallstones and of the symptoms produced by them appeared in the sixteenth century although in early Jewish writings there is said to be some mention of them Hoppe Seyler[97] whose historical summary on the subject is one of the best available felt that gallstones were perhaps less common in ancient times than they are today presumably because of dietary and environmental factors Most modern pathologists put the incidence of

present and indifferent if severe pain has not been noted In the group as a whole actual biliary colic is a relatively infrequent symptom and is mentioned by only approximately 25 per cent of patients Constant dull pain in the right upper abdominal quadrant, often aggravated by the taking of food, is a common symptom, it should not be confused with true colic There may be nocturnal exacerbations of this type of pain, and it may be definitely aggravated by jarring or jolting Immerman[91] has particularly emphasized the significance of long continued dull pain in the region of the gallbladder Practically all patients have a more or less specific intolerance to fats, coarse foods and heavy meals many of them are afraid to eat because of postprandial distress and they lose weight for this reason Gaseous indigestion with bloating and belching is a common symptom and often cannot be attributed to any particular type of food Regurgitation of food, pyrosis and even nausea and vomiting constitute the syndrome of 'reverse peristalsis which Alvarez and his collaborators[9] have described as often associated with chronic noncalculous cholecystic disease

A type of dyspepsia very closely simulating that of ulcer may be encountered in about 25 per cent of cases Constipation of the spastic" type is very common intermittent periods of irritability of the bowel may be associated, and occasionally patients describe episodes of diarrhea Fever of low grade has been a feature of some cases especially of those with pronounced associated infection of the bile passages Slight, transient jaundice may occur presumably because of associated hepatitis, but it is relatively uncommon. Joint disturbances ranging from periarticular arthritis and fibrositis to frank infectious arthritis have been considered a feature of some diagnostic importance, but it is doubtful if such symptoms are referable to the gallbladder, as patients in the age groups under consideration are liable to such complaints

In general the severity of the symptoms in cases of noncalculous cholecystic disease is definitely less than in cases in which patients have cholelithiasis, but interpretation of this fact depends to a great extent on the sensitivity of the individual affected A hypersensitive, neurasthenic individual with minor degrees of cholecystitis suffers more or at least has more complaints than the stolid, hyposensitive individual with stones An imposing list of associated symptoms has been mentioned by various writers among which may be mentioned, vague biliousness easy fatigability various subjective nervous disorders cardiac and vasomotor disturbances chronic lesions of the skin, disturbances in vision vertigo and headache Just how much these symptoms have to do with cholecystic disease and how much to a hypersensitive nervous mechanism is debatable

The associated physical findings of noncalculous cholecystic disease are meager The frequent association of oral foci of infection or chronic inflam

a new and very large soft cholesterin stone comprising almost a complete cast of the gallbladder

Pathogenesis of Gallstones

There are few subjects in medicine about which there has been so much loose thought and writing as about the mechanism by which gallstones are formed As Rous and his collaborators[103] have stated the literature is top-heavy with hypothesis and dismal with uncorrelated observations Much of the earlier work is rendered valueless by inadequate methods and many later studies have been carried out without reference to other and conflicting theories of the formation of gallstones There are certain general factors in the production of gallstones which have been mentioned (1) biliary stasis in the gallbladder presumably brought about by visceroptosis physical inactivity and biliary dyskinesia (2) diet almost every imaginable type of dietary error having been charged with the formation of gallstones a prolonged high intake of cholesterol probably being of some importance (3) pregnancy and although Gross[33] and Hosoi and Alvarez[40] do not feel that the high incidence in women is related to this factor the unusually high incidence of gallstones in women who have borne children has been emphasized in the past (4) obesity 90 per cent. of Mentzer's[77] patients who weighed more than 00 pounds having gallstones and (5) hepatic disease It seems probable that hepatic dysfunction from whatever source is definitely related to the pathogenesis of stones for example stones are not infrequently found in individuals with cirrhosis or chronic hepatitis of long standing The recent observations of Rozendaal and his collaborators[102] on the relation of minor disturbances in the excretory function of the liver and cholecystic disease should be mentioned in this connection

The principal specific theories of the pathogenesis of stones have been critically examined by Mentzer[104] Newman[11] and by Rous and his associates[103] and the reader is referred to their articles for a more detailed discussion and for bibliographic references Only the more important theories as to the formation of gallstones can be given here

Stasis Theory — The stasis theory is attractive in a few respects gall stones are exceedingly rare in animals both wild and domestic presumably because of their more active state Bilirubin-calcium stones have been produced in the distended gallbladder of dogs by ligation of the cystic duct. There are some theoretical objections to the work however and it appears that stasis cannot often be a primary factor

Infection Theory — The concept of lithogenous catarrh as advanced by Naunyn[106] and affirmed by Aschoff and Bacmeister[100], is still looked upon as

gallstones in the adult population at from 5 to 20 per cent, and it is generally agreed by surgical authorities that from 50 to 90 per cent of all cholecystic disease is associated with the presence of stones. Kehr[36] believed that about 10 per cent of all adults have stones, and Cross[39], whose material is based on 9,531 autopsies, found stones in 8.4 per cent. Mosher[98] found that 8 per cent of adults in the fourth decade of life had stones, and that the incidence rose to 13 per cent in the fifth and sixth decades. Mentzer[7] in 633 postmortem examinations at the Mayo Clinic reported that 21.7 per cent of adults had cholelithiasis. Crump[99] in a series of 1,000 necropsies found stones in the biliary tract in 32.5 per cent, and he stated that after the seventh decade of life the incidence was 50 per cent. All American and European writers agree on the predominance of cholelithiasis in women, stones being found two to five times as often as in men, a rising incidence with age and also a diminishing sex ratio is generally agreed on. It is of some interest to note that calculi have been found in the gallbladders of newborn infants and nurslings, but in general the incidence during adolescence is remarkably low.

Classification of Gallstones

The usual morphologic classification of stones is essentially that suggested by Aschoff and Bacmeister[100]: (1) the common or inflammatory stone of the gallbladder consisting of a mixture of cholesterin, bile pigment and fractional amounts of various salts, this first type being the one most commonly encountered and the one that made up 73 per cent of Crump's[99] series, (2) the pure bilirubin calcium stone which rarely contains significant amounts of cholesterol, (3) the pure cholesterol stone, (4) the combination stone, containing various amounts of bilirubin calcium salts and cholesterol, and (5) the calcium carbonate stone.

The number of stones which may form in the gallbladder, may be very large, as many as 14,000 having been found. Very large stones are seen occasionally and one weighing 110 grams has been reported. The stones found in an individual case may not be of the same type, but as a rule most of the stones encountered seem to represent a single crop. Cholesterin stones may be found in company with so called common gallstones. The time required for the formation of stones probably is short. Cameron[101] has mentioned a case in which stones formed within two months and Harries[10] has described a similar case in which pure cholesterin stones probably developed within three months. Calcium bilirubinate concretions may form in the bile passages of experimental animals within three weeks[103]. Mentzer[104] has noted an interesting case in which the gallbladder which had previously been observed at laparotomy and found to contain two stones, was found at necropsy a few days later to contain

bile acid ratio at or near the precipitation level may be secreted Exner and Heyrovsky[116] have assumed that bacterial action decomposes bile salts and thus favors precipitation of cholesterol The mechanics of the process of precipitation have recently been discussed by Weiser and Gray[117], who concluded that precipitation takes place around fat droplets in the bile

The principal difficulty which arises in connection with this theory is that infection appears to play a part in the process While it is quite true that many large pure cholesterin stones are found in gallbladders which show no appreciable inflammatory change or at most minor degrees of cholesterol deposition in the mucosa the possibility of a previous inflammatory process cannot be excluded entirely It seems evident that even minor and transient inflammatory changes in the wall of the gallbladder might affect the properties of the mucosa as a concentrating and absorbing surface sufficiently to allow for the precipitation of cholesterol It is of interest to note that the gallbladder of normal dogs will absorb some gallstones from man[118]

Nucleus Theory — Gallstones as a rule have a definite nucleus which may consist of an agglomeration of bacteria epithelial debris mucous plugs and occasionally such foreign bodies as suture material Mentzer[104] and others mention ascaris and portions of distoma hepaticum as a nucleus for stones Occasionally a stone of one type will form over a small calculous deposit of entirely different material The nuclei most commonly found in stones resemble bile thrombi in their general properties their exact chemical composition is unknown Rous and his collaborators[119] have observed these deposits in their physiologic studies on intubation of the biliary system Rovsing[120] suggested that such bile thrombi might form in the intrahepatic ducts and be washed into the gallbladder Apparently in human subjects and in experimental animals deposits of pigment of the type usually found in the nucleus of gallstones can form in the absence of stasis infection or other factors in both man and animals[119] such deposits have been found on drainage tubes which have been left in the biliary tract for long periods In congenital hemolytic icterus repeated crops of pigment stones may form in the bile passages I have records of one case in which the common duct was occluded three times by such deposits

A discussion of the formation of gallstones would be incomplete without some reference to the composition of gallbladder bile since in the light of recent work it appears very probable that changes in its physiochemical properties brought about by changes in the concentrating activity of the gallbladder which in turn probably depends on infection or toxic damage to the mucosa of the gallbladder, have a great deal to do with the formation of stones It may be conceded that nuclei around which stones may form can be deposited in the gallbladder by means of inflammatory or degenerative processes in the

perhaps the most important single cause of the formation of stones Certainly a very large number of stones must form as a result of previous infection of the gallbladder, possibly because of disturbances in the chemistry of bile brought about by changes in the concentrating activities of the organ The frequency with which pathogenic organisms can be recovered from the wall of the calculous gallbladder, from bile and from stones gives added weight to this hypothesis The reformation of stones in a gallbladder previously opened and drained also suggests the importance of residual infection It is claimed that gallstones have been produced experimentally by the intravenous injection of such organisms as streptococci, but this work has not been generally accepted The methods by which infection can act to produce stones will be apparent from subsequent paragraphs The work of Rous and his collaborators[106] who produced stones in dogs in the absence of stasis, infection and cholecystic influence, is the strongest argument against the infection theory

Hypercholesterolemia Theory — This theory is based on the idea that there may be an aseptic precipitation of cholesterol within the gallbladder presumably owing to a high content of cholesterol in the blood and bile, which in turn is dependent on hypercholesterolemia Wilensky[107], Dewey[108] and other investigators have contributed evidence in favor of this theory Elevation of blood cholesterol may be brought about by a variety of conditions, of which pregnancy is probably the most common[109] in post infectious states in conditions associated with lowered basal metabolism, in nephritis, and according to some observers[110] in certain types of hepatic and cholecystic disease abnormally high values for blood cholesterol have been obtained Hypertrophy of the suprarenal cortex and increased activity on the part of the corpus luteum have also been mentioned as possible causes Dietary factors appear to be of some importance A high intake of cholesterol has been found experimentally to be effective in producing cholesterol deposits in the gallbladder, presumably by elevating the cholesterol concentration in bile this work however has not been generally accepted

Assuming that the concentration of cholesterol in the bile is increased the means whereby it is precipitated have yet to be explained It appears to be held in solution by the formation of water soluble addition compounds by virtue of the presence of bile acids It has been assumed that in the presence of certain pathologic conditions of the mucosa of the gallbladder bile acids will be absorbed from the gallbladder more readily than cholesterol, thus reducing the bile salt cholesterol ratio which is normally about 18 to 1, and causing the precipitation of cholesterol Such low ratios have been encountered in the bile obtained from pathologic gallbladders by Rosenthal and Licht[111], Newman[112], Andrews and others[113] Andrews and his associates[114 115] have also reported that in the presence of hepatic dysfunction bile with a cholesterol

in aged persons who have never suffered from them Kehr[3] felt that the number which are productive of symptoms may be as low as 5 per cent Barker[10] felt that 10 per cent is a more likely figure Moynihan[18] felt that the incidence of symptoms in the presence of stones is much higher and that there are few patients with calculi in their gallbladders who do not at least have some dyspeptic symptoms W J Mayo[17] has stated his somewhat similar views in an article entitled Innocent Gallstones a Myth

The situation of stones in the biliary tract obviously has a great deal to do with the nature of the symptoms complained of In something more than half of all patients with stones such stones are confined to the gallbladder alone in from 10 to 15 per cent. the gallbladder and cystic duct contain stones and the association of stones in the gallbladder and common duct occurs with approximately the same frequency In about 6 per cent of cases of cholelithiasis the common duct alone is found at the time of operation to be involved

Pathological Changes

Baumgartner[69] in analyzing a series of 4 575 gallbladders removed at operation gave some interesting figures that indicate how frequently stones are associated with cholecystic disease of all types In cases of chronic catarrhal cholecystitis stones were found in 60 per cent in strawberry gallbladders in 50 per cent and in chronic fibrous cholecystitis and in the acute and subacute varieties of cholecystitis in about 90 per cent In the presence of empyema hydrops gangrene and malignancy the incidence of stones averaged about 96 per cent Since gallbladders affected by chronic cholecystitis and cholesterosis make up about 65 per cent of all gallbladders removed surgically it can be seen how extensively stones enter into the picture of clinical cholecystic disease

Obviously the pathologic features are extremely variable in general they are those of the various types of cholecystitis described in an earlier paragraph plus the added feature of the presence of a foreign body The general effects of stones may be classed as infective and mechanical Recurrent infection of the biliary tract so frequently associated with the presence of stones will produce a mixed picture of subacute and chronic cholecystitis with progressive destruction of the mucous membrane thickening of the walls and pericholecystitis In many instances the surgeon finds the gallbladder functionless thick walled and contracted down upon its contents When the cystic duct is occluded by stone opportunities for further calculous formation are increased hydropic distention of the gallbladder may occur and layers of calcium carbonate may be precipitated about other stones already present in the organ. The opportunities for infection likewise are increased by occlusion of the cystic

liver, gallbladder, or ducts the presence of such particulate matter in so complex a compound as bile might easily serve to precipitate cholesterol or calcium bilirubinate. The presence of alterations in the colloidal properties of bile as a basis for the formation of stone were first suggested by Lichtwitz[11,12], and there is much to indicate that some aspects of the theory may be sound. For instance, alterations in the acidity of bile might be of considerable importance in causing precipitation, since Rous, McMaster and Drury[13] have shown that the known acidity of the bile is sufficient to keep some of its constituents in solution, whereas a change in p^H in the opposite direction may tend to precipitate calcium salts and cholesterol. That such changes in the reaction of bile do occur has been shown in experimental animals and in man. Changes in the permeability of the wall of the gallbladder will produce, as Ravdin and his coworkers[17] have shown, a diminution in the concentration of bile salts in bile, with or without a fall in its cholesterol content. Under such conditions the chloride and bicarbonate ions increase thus rendering the bile more acid whereas the calcium content may diminish below the level found in normal hepatic bile, and the total base decreases. These changes result in optimal conditions for the precipitation of some of the relatively unstable compounds in bile. It is probably along these lines that further studies on the etiology of gallstones can be directed with the greatest prospect of success.

The rare calcium carbonate stone probably constitutes a special case in the matter of bile chemistry. Such stones appear to be formed almost exclusively in the presence of complete obstruction of the cystic duct. Under these conditions calcium carbonate appears to enter the gallbladder in large amounts and may form soft, white stones a paste or the so-called "Kalkmilchgalle." In the presence of such stones the degree of cholecystitis usually observed is mild rather than severe. The chemistry of the process is not understood. It has been suggested that calcium salts enter the gallbladder with considerable quantities of fluid which later is reabsorbed with resulting precipitation of the calcium. The subject has been reviewed recently by Phemister and his associates[14] and the reader is referred to their articles for further details.

Cholelithiasis and Calculous Forms of Cholecystitis

The high incidence with which gallstones are found in the general population has been mentioned already. Rare in individuals under the age of thirty years, they are very frequently found in older individuals of both sexes, the incidence increasing with age. Unfortunately there are no figures available which indicate how many of these stones produce symptoms, certainly many are, for all practical purposes silent, and it is very common to encounter stones

distress in the upper part of the abdomen a sense of oppression confined to the epigastrium often relieved by belching or vomiting and vague nausea and flatulence are among those mentioned most often These symptoms appear at varying intervals after the taking of food and are as a rule aggravated by coarse or greasy articles of diet Sometimes peptic ulcer is simulated pyrosis and epigastric burning are noted after meals but the regular time sequences so characteristic of ulcer may be lacking Constipation intestinal irritability and bouts of diarrhea often are troublesome Pericholecystic adhesions may involve the duodenum and pylorus and introduce an element of mechanical difficulty in the emptying of the stomach

The fact that peptic ulcer and gallstones frequently coexist adds to the difficulty of diagnosis many patients with ulcer may present symptoms which are difficult to control the subsequent detection of a stone filled gallbladder often leading to a solution of the therapeutic problem

In many cases indigestion usually will follow the eating of certain coarse rough or greasy foods This food selection or the so-called qualitative type of dyspepsia is a common accompaniment of gallstones of itself it is not diagnostic but it is frequently volunteered by the patient as the principal complaint One often sees patients who have reduced their diet gradually omitting one article of food at a time in the hope of avoiding postprandial distress in such cases a very limited and peculiar dietary may be adopted eventually and nutrition suffers accordingly

Dull constant pain in the region of the gallbladder is another common complaint it does not approach the severity of a true colic and more frequently is of an aching or rheumatic type Radiation of pain to the chest and right arm is said to occur Pain also may be confined to the region of the lower ribs posteriorly and has been mistaken for lumbago Jolting and jarring aggravate distress of this type and patients often complain of their inability to sit back comfortably when riding in an automobile

Absorption of toxic material from an infected gallbladder may contribute to the production of arthritic symptoms and it is not uncommon to encounter arthritis of various types particularly periarticular fibrositis among patients with cholelithiasis Fever of low grade and general mild systemic manifestations of infection may also be attributed to absorption from a diseased gallbladder Slight jaundice resulting from hepatitis and cholangeitis is relatively rare but there are certain cases in which intermittent jaundice resembling the so-called toxic or infectious variety seems to depend on the presence of stones

Biliary Colic — There is no general agreement as to the exact mechanism by which biliary colic is produced nor as to the nervous pathways by which the painful sensations are conveyed The usual explanation is that pain is produced by the contraction of the gallbladder on its contents or against the

duct, and acute and chronic empyema of the gallbladder are common sequelæ Diverticula of the wall of the gallbladder or of the cystic duct may form in the presence of stone Fistulas into other organs almost invariably result from ulceration of stones through the wall of the gallbladder The invasion of the digestive tract by stones may lead to obstruction, if the stones gain entrance to the common duct, obstructive jaundice may supervene The association of hepatitis cholangeitis and pancreatitis with the infective forms of cholecystitis has been mentioned already, stones merely adding to the severity of the process Ulceration of the mucous membrane of the bile passages by stone may lead to local hemorrhage, and there are cases on record in which profuse bleeding took place from associated areas of duodenitis It must be admitted however that the source of the occasional gastrointestinal hemorrhage associated with stones is somewhat obscure It should be emphasized that there is no uniform relation between the severity of the infectious process in the wall of the gallbladder and in the ducts the size, number and type of stones and the clinical picture produced by their presence

Symptoms of Cholelithiasis

The clinical syndromes associated with cholelithiasis are virtually innumerable as one might expect from the numerous pathologic conditions of the gallbladder associated with them and the known high incidence of complicating conditions Rolleston[1 8] has considered them under five headings, (1) the masked or inaugural symptoms (2) biliary colic (3) mechanical effects (4) inflammatory and infective sequelæ, and (5) fistulas connecting the gallbladder with other organs It is impossible to make as sharp a distinction as is suggested by this classification but it is of some use in simplifying the discussion to follow

Masked or Inaugural Symptoms —It seems probable that the so-called inaugural symptoms of stones[128] are essentially those of associated cholecystitis, which have been enumerated already and need not be considered here in great detail Hurst[1 9] particularly emphasized the fullness and digestive distress which follows a full meal the variability in time element between the taking of food and the onset of distress the frequent nausea and vomiting without relief and the irritability of the large bowel He has also commented on the ulcer like symptoms which may arise as well as on the fact that such symptoms are not significantly improved by the usual methods of ulcer management, in general, they are more severe and persistent than those associated with non calculous cholecystic disease and often persist for years with relapses and remissions, not infrequently punctuated by biliary colics The commonest of the so-called masked symptoms are those of an obstinate dyspepsia fullness

breath is common. The pulse rate as a rule is not greatly increased but it may rise as inflammatory processes supervene Belching nausea and vomiting are common accompaniments of the pain the vomiting may be intractable particularly if a stone becomes impacted in the cystic or common duct Rigor and fever are common accompaniments even of uncomplicated colic

Morphine in considerable amounts usually is required for relief milder colics may respond to barbiturates or exceptionally to amyl nitrite The duration of the attack usually is brief particularly if morphine is given Pain which lasts for several hours or days may be taken to indicate the development of an inflammatory process in the gallbladder or impaction of stone in the cystic duct

Usually it is a difficult matter to make a satisfactory examination of the abdomen during actual colic The liver may be found to be enlarged and the region of the gallbladder exquisitely tender there is often considerable spasm of the right rectus muscle Reexamination of the region of the gallbladder after an attack of colic may give useful information Residual deep tenderness a common sequel of colic probably is an expression of an inflammatory process in the wall of the gallbladder Cutaneous hyperesthesia often is noted following an attack usually it is most pronounced over the region of the gallbladder Fever and leukocytosis are noted in about 50 per cent of cases if these persist the onset of a suppurative process empyema or gangrene should be suspected If the stone remains impacted in the cystic duct there may be resultant dilatation of the gallbladder with hydrops or with an associated inflammatory reaction and the gallbladder may therefore become palpable Slight scleral icterus and bile stained urine after biliary colic suggests but does not necessarily indicate the presence of a stone in the common duct. The symptoms and sequelæ of this condition will be discussed in a later section

Mechanical Effects of Gallstones

Stones may cause symptoms of mechanical origin when because of their size and the position of the gallbladder they impinge upon adjacent structures Cases have been recorded in which symptoms produced by a distended and stone filled gallbladder pressing on the pylorus have closely mimicked gastric cancer Pressure on the portal vein has been said to cause portal thrombosis but as Rolleston[18] pointed out when symptoms of pressure are present usually there are masses of adhesions around the gallbladder and ducts which complicate the process considerably At present it is rare to find stones in the gallbladder of sufficient size to produce true mechanical disturbances of this type Occasionally a gallbladder containing stones may be angulated and bound down to the common duct in such a manner that distention or infection

back pressure offered by the sphincteric mechanisms in the neck of the gall bladder or at the end of the common duct If mechanical obstruction to the cystic or common duct is present, as usually is the case when stones are present this explanation seems to fit the facts The concept of a 'functional' type of colic is not so easily understood, but there is good physiologic evidence to show that such a condition exists This evidence has been discussed in an earlier paragraph under the heading of "biliary dyskinesia" It should be emphasized that colic is not diagnostic of the presence of stones, and that even if stones are present a painful seizure does not necessarily mean that calculous material is being expelled from the gallbladder

Biliary colic is one of the most striking of all clinical symptoms and if present in its typical form, can rarely be confused with the pain produced by another ailment While it may be independent of the presence of stone it is induced most frequently by the presence of calculous material somewhere within the gallbladder or ducts Colic may be spontaneous, it also appears to be brought on by a variety of causes namely, jolting jarring, an unusually heavy meal, medical examination including cholecystography and possibly by the development of minor intercurrent infectious processes which excite the gallbladder to contraction Nocturnal seizures are common and quite characteristic of the condition The pain has been described as 'the most intense that attacks mankind' It has often been said by those who have had personal experience that it greatly exceeds the pains of labor As a rule the distress is paroxysmal in character, it may begin very abruptly and continue with frequent brief periods of partial relief followed by further seizures of pain It often passes off as suddenly as it began even when no narcotics have been given The situation of the pain is variable[130], a point which has not been sufficiently emphasized The usual site of origin is the epigastrium or a point in the right upper quadrant of the abdomen corresponding to the situation of the gallbladder Pain may begin in the back and radiate anteriorly however, pain on the left side is not particularly uncommon and it has been suggested by Libman[131] that contralateral pain of this type is more commonly noted in hyposensitive individuals Radiation of pain to the chest may occur thus simulating angina pectoris most frequently, however, the pain radiates around the lower ribs to a point beneath the right scapula Intense, boring through and through pain radiating to this same point is described sometimes Radiation to the point of the right shoulder is somewhat uncommon and, if present, usually is due to peritoneal involvement in the region of the gallbladder with irritation of the diaphragm

The behavior of patients during biliary colic is of some importance The affected individual frequently writhes about in agony, perspires profusely and often has a definite rigor Respiratory embarrassment and a 'catch in the

pancreatitis there are no pathognomonic symptoms Elevation of the value for serum lipase may as Comfort and Osterberg[133] have shown be of considerable diagnostic importance

One mechanical effect of stones which is rarely seen nowadays is intestinal obstruction gallstones in the intestinal tract being apparently a much more common phenomenon in the days when the gallbladder was seldom operated on and when it was the practice to sift the stools after biliary colic to determine whether stones had passed At present actual intestinal obstruction from stone is seen rarely obstruction in not more than 1 or 2 per cent of cases *being due to this cause* Wagner[134] *reported 334 cases in 1914 most of them* from the earlier literature, Angle[135] has described two recent cases and reviewed the more recent reports

Stones may possibly migrate through the cystic and common duct into the bowel but this route of entry certainly is encountered seldom in present day practice the usual method of entry of gallstones into the intestinal tract being by way of a fistula which in turn arises from an ulcerative process in the wall of the gallbladder Calculi whether single or multiple may pass into the bowel without any striking symptoms other than those attended with biliary colic and subsequent acute or subacute cholecystitis It has been said that stones may lie latent in the bowel for long periods and there increase in size by the deposition of salts It appears that stones may cause obstruction anywhere in the gastrointestinal tract the most common site being in the small intestine particularly at the lower end of the ileum a few inches above the valve *They may also become impacted at points where the intestine is* angulated or bound down by adhesions Very large stones, or a collection of *smaller stones may obstruct the sigmoid flexure especially if they have entered* the bowel by way of a cholecyst-colonic fistula

The clinical symptoms of the condition are not characteristic and an accurate diagnosis rarely is made The affected individuals are as a rule past fifty years of age Females are said to be affected about five times as often as males The clinical picture is that of intestinal obstruction which usually has been preceded by biliary colic or by other evidence of antecedent cholecystic disease Bloody vomitus may be produced by bleeding from the fistulous tract It is said that in about half the cases the patients spontaneously rid themselves of stone in the bowel however this fortunate turn of events cannot be depended upon and the proper treatment is surgical

Inflammatory or Infective Effects of Gallstones

In the section on cholecystitis it was stated that the walls of chronically infected and stone containing gallbladders frequently yielded bacteria on

will compress the duct and cause obstructive jaundice a large stone in the cystic duct may have the same effect

The mechanical effects of stones within the ducts are of considerably greater clinical importance Rupture as a result of back pressure is very rare. When in the absence of infection the cystic duct is obstructed by a calculus, the gallbladder becomes greatly distended the bile pigments may be gradually absorbed whereas the outpouring of mucoid secretion from the mucosa converts the structure into a mucous cyst In cases of hydrops formed in this way the gallbladder may reach great size and contain a liter or more of fluid and debris occasionally such gallbladders have been confused with pancreatic, mesenteric or ovarian cysts The first cholecystostomy performed in this country, that described by Bobbs, was done under the impression that a cyst was being drained A hydropic gallbladder may partially empty itself and later refill after the fashion of intermittent hydronephrosis It has been said previously that calcium may be excreted into a gallbladder, the cystic duct of which has been occluded and it is under these circumstances that calcium stones and milk of calcium bile is formed also quantities of calcium may be deposited in the walls On palpation a hydropic gallbladder has a distinct cystic feel it is moveable and often not very tender, its situation and the patient's history usually serve to identify the condition Occasionally a distended stone filled and calcified gallbladder is seen, which is hard fixed, tender and, therefore strongly suggestive of malignant involvement

If stones reach the common duct the general mechanical effects on the intrahepatic and extrahepatic bile passages are much the same, the usual sequel is obstructive jaundice There is distention of the entire biliary tree, which because of the suppression of biliary flow and of the mucoid secretion of the ducts may be productive of a system filled with 'white bile [17]' The clinical picture of stone in the common duct is considered in detail in the section of diseases of the bile ducts, it suffices to say here that aseptic obstruction from stone is rare and that the process ordinarily is complicated by infection and fibrosis

The pancreas sometimes may be involved by stones in the ampulla In certain individuals the pancreatic ducts open into the common duct in such a manner that a low lying stone in the common duct will occlude the pancreatic ducts directly or allow for a reflux of bile into them Under such conditions cystic dilatation or rupture of the pancreatic ducts may take place in the latter event acute pancreatic necrosis may occur More commonly chronic induration and edema of the head of the pancreas are found

The diagnosis of pancreatic involvement resulting from the mechanical effects of stones is difficult extreme pain shock like prostration and a rigid abdomen signify pancreatic necrosis in the more common condition of 'chronic

the gallbladder into the peritoneal cavity and walled off by adhesions in such cases local abscesses may be present

Such fistulous connections between the biliary tract and other internal organs are produced almost exclusively by the migration of gallstones causing local ulceration of the wall of the gallbladder and subsequent necrosis inflammatory noncalculous cholecystic disease does not appear to be responsible except in very rare instances While stones may not be demonstrated always at operation or at necropsy in connection with such fistulous tracts usually there is evidence to indicate their presence at an earlier date Occasionally ulcerating lesions of the stomach duodenum or colon may perforate into the gallbladder thus forming a fistula in a retrograde direction leading to secondary infection of the bile passages Most internal fistulas lead from the gallbladder and much less frequently from the common or cystic duct the fundus of the gallbladder being a favorite site of origin A majority of fistulas connect with the duodenum, the colon and stomach ranking second and third respectively In the older literature there are reports of fistulous connections with a large number of abdominal organs gallstones have been found in the bronchi the pleural cavities the kidney pelves the urinary bladder the pregnant uterus and even in ovarian cysts Ordinarily however only fistulous connections with the intestinal tract need be considered.

The usual history is that of severe and long continued cholecystic disease with colic jaundice and related symptoms which are more or less miraculously relieved after a severe attack indicating that the gallbladder had emptied its contents into the intestinal tract Such fistulas tend to close eventually unless they are very large or unless the cystic or common duct is occluded At operation healed fistulas are commonly found if a patent fistula is present the gallbladder usually is shrunken and may contain infected bile stones duodenal contents and gas.

Diagnosis of an internal biliary fistula rarely is possible unless stones are passed by bowel In two cases in Judd and Burden's[146] series a barium enema revealed a fistulous connection with the colon rarely is a cholecystoduodenal fistula made out during roentgenologic examination of the barium filled stomach For obvious reasons cholecystography is of no diagnostic value under these conditions The principal importance of such internal fistulas lies in the fact that in their presence cholecystectomy carries a somewhat increased risk peritonitis being a fairly frequent complication.

External Fistulas

External biliary fistulas may be spontaneous but they result much more often from a previous operative procedure *Spontaneous external fistulas may* be regarded as curiosities and are seen rarely in modern practice Cases are

culture The presence of stones may result in a lighting up of this latent infection and lead to a cholecystitis which is characterized by progressively increasing damage to both the mucosa of the gallbladder and its walls Chronic fibrous cholecystitis in which the greatly thickened gallbladder is firmly contracted down on its calculous contents, is the most common result when the cystic duct is irritated by stones impacted in it, it also may undergo fibrosis and become partially occluded The presence of stones in either the gallbladder or cystic duct may if infection is present, lead to suppuration and to the formation of empyema which is usually a chronic rather than an acute process Acute and subacute cholecystitis have been described already both conditions are associated with the presence of stones in an overwhelming majority of cases When biliary colic is followed by severe and continuous pain by rigidity of the right rectus muscle and by increasing tenderness in the right upper abdominal quadrant, the development of acute cholecystitis may be suspected. Persistent fever rigors and vomiting are common accompaniments In cases of acute cholecystitis of unusual severity gangrenous or phlegmonous changes may take place Perforation of a suppurative cholecystitis, fortunately does not often occur when it does the result may be general peritonitis, more often however, a walled off abscess forms, which may partially resolve or discharge its contents into an adjacent viscus Most broncho-biliary fistulas owe their origin to such a course of events, and many internal fistulas from the gallbladder also form in this manner

The infective results of stone in the common duct are considered in a later section As is the case when obstruction and infection combine to involve the gallbladder, the result may be acute suppuration or more often chronic fibrosis of the extrahepatic and intrahepatic bile passages The same statement may be made of occlusion of the pancreatic duct by stones with associated infection it is believed that some pancreatic cysts are formed following such episodes of pancreatitis

Biliary Fistulas

Internal Fistulas

Fistulas which follow ulceration of the wall of the gallbladder and expulsion of stone into the intestinal tract are encountered infrequently in present day practice spontaneous external biliary fistulas are even more uncommon. Naunyn[106] reported 384 cases from the older literature, in nearly half of which the fistula was external The only type of fistulas which are seen with any frequency at present are those which form between the gallbladder and the duodenum or colon, and most of these are found unexpectedly at operation or at necropsy

Occasionally the surgeon encounters stones which have been extruded from

LABORATORY DATA IN THE DIAGNOSIS OF CHOLECYSTIC DISEASE

Before considering the general problem of diagnosis of the calculous and noncalculous forms of cholecystitis laboratory procedures on which much reliance is now placed may be considered. For the most part the diagnosis of cholecystic disease should depend as much on clinical acumen as on data obtained from the laboratory The experience of the last few years seems to *indicate that refinements in diagnosis are drawing into the diagnostic net* a considerable number of patients with minor degrees of cholecystitis and stones, which virtually are asymptomatic In such cases the benefits derived from operation are not great For this reason alone one should not lose sight of the patient s complaints and should remain critical of a purely laboratory diagnosis

Cholecystography developed scarcely more than ten years ago by Graham and Cole[144] has become an established aid in the diagnosis of biliary disease For a fuller discussion of its uses and limitations the reader is referred to a monograph by Graham and others[145] The original administration of the cholecystographic medium intravenously has in general been superseded by its oral administration As Palmer and Ferguson[146] have shown reactions following its intravenous administration may be of considerable magnitude The procedure recommended by Kirklin[147] is as follows Special preparation of the patient is unnecessary but the taking of purgatives or other medicines shortly before or during the test is not permitted Four grams of the sodium salt of tetraiodophenolphthalein freshly dissolved in 30 c c of distilled water is given to the patient. He is instructed to eat a substantial meal at six o clock but one containing a minimum of butter cream eggs or other fats and immediately afterward to take the entire dose of dye in a glassful of grape juice orange juice or carbonated water He is also directed to cleanse the bowel next morning with saline enemas and to abstain from breakfast although he is allowed to have black coffee or clear tea and may drink water as desired Roentgenograms are made at 8.00 A.M. and again at 10 00 A M. With his luncheon at noon the patient is required to take a glassful of equal parts of milk and cream A third set of roentgenograms is made at 2.00 P M

Almost invariably the normal gallbladder casts a definite, regularly outlined homogeneous shadow which varies in size and density in the successive films Ordinarily the shadow is of good density in the first set slightly larger and denser in the second and smallest and densest in the third, but this sequence is by no means constant Neither a standard size nor a standard density can be prescribed and unless the shadow is exceedingly faint it should be considered normal in this regard In short judgment of the normal should be liberal rather than strict Neither the general form nor the position of the shadow are

recorded in which a fistula formed and extruded gallstones at various points in the thorax or abdominal wall or even in the groin The usual site is at or near the umbilicus, the falciform ligament probably directing the course of the fistula to this point Postoperative biliary fistulas are almost invariably referable to a persistent obstruction somewhere along the course of the extrahepatic biliary passages, most frequently the common duct, or to the presence of all or part of the gallbladder In a series of 166 cases reported by Balfour and Ross[137] gallstones or their complications were responsible for the fistula in 85 per cent. In a majority of their cases the gallbladder had not been removed but only drained by cholecystostomy in others partial cholecystectomy had been performed In still other cases the persistence of the fistula was explained on the basis of stone stricture pancreatitis, or neoplasm obstructing the bile ducts A persistently draining fistula usually can be taken to indicate permanent obstruction, one which drains intermittently and closes is due most frequently to residual stone The occurrence of fistulas in connection with stricture of the common duct will be discussed in a subsequent paragraph Injection of the fistula with radiopaque oil, as suggested by Gabriel[138], Overholt[139], Thorlakson and McMillan[140], Walters and Thiessen[141] and others, may yield valuable information as to the cause and site of obstruction and may serve as a guide to proper treatment

The effects of long continued external biliary drainage on the affected individual are of some importance, in experimental animals external fistulas lead to serious nutritional disturbances osteoporosis and spontaneous fractures In human subjects the loss of bile is somewhat less likely to produce serious effects as shown by Bernays[14] case of eleven years duration, however the loss of minerals interference with digestion of fat and the loss of fat soluble vitamin secondary to external biliary drainage may interfere ultimately with nutrition[143] The feeding of bile by mouth appears to be of some value in correcting these conditions the discharge from the fistula can be collected and replaced by duodenal intubation The dilatation and infection of bile passages, which accompany external fistulas may lead to hepatic dysfunction as shown by appropriate testing of liver function with bromsulphalein

Treatment of external fistulas is wholly surgical, the removal of any obstruction to the ducts being the first consideration, since if this is accomplished spontaneous closure may be expected to occur If obstruction to the common duct cannot be relieved transplantation of the fistula into the stomach or duodenum may be necessary It is important to exclude so far as possible, the presence of malignant obstructive lesions at the ampulla of Vater or elsewhere before operation is undertaken and for this reason it may be advisable to allow a sufficient interval of time to elapse after the formation of a fistula before attempting to repair it.

remaining instances an abnormal condition of the gallbladder will almost always be indicated by a very faint or absent shadow

It has been noted repeatedly that diagnosis on the basis of a faint cholecystographic shadow alone is somewhat insecure Such a faint shadow may be caused by vomiting of the dye a fatty meal producing premature evacuation of the gallbladder or exceptionally by failure of absorption from the intestine Cirrhosis and various forms of hepatitis may reduce the rate of elimination of dye and so affect the shadow In the presence of visible jaundice the diagnostic accuracy of faint or absent shadows must be questioned although occasionally the gallbladder also may confuse the issue a previously drained gallbladder may or may not fill and empty in a normal fashion

A negative cholecystogram also may be deceiving since a diseased gallbladder may preserve or regain its property of concentrating the cholecystographic dye Many gallbladders reported as normally functioning may contain stones some may have sustained previous attacks of acute cholecystitis and with regeneration of the mucosa may have been able to concentrate normally again In spite of the numerous sources of error the general accuracy of the method is surprisingly high Following a report of a nonfunctioning or poorly functioning gallbladder with or without stones the diagnosis of cholecystic disease is confirmed at operation in about 95 per cent of cases and stones are found in 75 per cent A diagnosis of a normally functioning gallbladder with stones is in the experience of most surgeons 99 per cent correct a diagnosis of a normally functioning gallbladder without stones if the technic is proper should rule out cholelithiasis although in about 10 per cent there is definite evidence of cholecystitis

In general the roentgenologist's report should be in terms primarily of function In other words he should report whether or not the gallbladder is able to receive or to concentrate the dye In addition he will note any evidence of gallstones or tumor If he is competent 90 per cent or more of his reports and diagnoses will prove to be correct Notwithstanding this degree of efficiency all roentgenologists warn that the final diagnosis should rest with the clinician who must correlate the roentgenologic findings with the history The cholecystographic data alone should never be made a basis for treatment or operation Formerly some attention was paid to the appearance of the stomach and duodenum at fluoroscopy with the idea that deformities and abnormalities of motor function were diagnostic of cholecystic disease this practice at present has been largely abandoned

There are other laboratory findings in cholecystic disease which deserve brief mention *Examination of the urine* ordinarily shows little of consequence from the standpoint of diagnosis During episodes of acute cholecystitis or following a protracted biliary colic there may be temporary albuminuria and

of clinical significance, since they vary greatly with the build of the patient. Hour glass deformities may be, but are not necessarily, pathologic, the diagnosis of pericholecystic adhesions by this means is rarely upheld by the operating surgeon A normal cholecystographic response signifies only that the gallbladder is able to receive and concentrate bile and is thus normal in respect to function, it does not preclude the existence of biliary disease Evidence now at hand indicates that in from 10 to 12 per cent of cases, in which there is a normal response to the test the gallbladder nevertheless is diseased, and this constitutes the greatest factor of error in cholecystographic diagnosis A shadow of the gallbladder, which has the same size and density during the period of the examination is probably caused not by the presence of concentrated dye but by thickening of the wall of the gallbladder or changes in its contents produced by disease After a day or two films should be made again without giving the dye to see if the same dense shadow is seen again

If the technic has been executed without error, absence of any shadow of the gallbladder shows that it is not functioning, and in 98 per cent of such cases this finding is indicative of cholecystic disease A faint shadow of the gallbladder so faint that effort is required to discern it, signifies marked interference with function and as a sign of disease, it is scarcely less reliable than complete absence of a shadow In the absence of a shadow or if the shadow is only faint inquiry should be made to determine whether or not the dye was vomited if the original dose was retained for thirty minutes or more, the results probably are valid A fat meal on the preceding evening also invalidates the result

Mottling of the shadow provided extraneous causes are excluded, as can easily be done is a dependable sign of gallstones or tumor of the gallbladder Mottling may be caused by gas in the bowel by calcification in the costal cartilages by transverse processes of the spinal column, or by concretions in the pancreas or kidney any of which may be in line with the gallbladder As a rule the shadow of any of these simulants will be projected outside the shadow of the gallbladder in some of the cholecystograms and thus will be recognized as of extraneous origin

Gallstones often are evident in the absence of any shadow of dye Those containing calcium produce proportionately dense shadows Even the cholesterol stones if they have a coating of calcium or are immersed in dense bile, may be apparent when there is no shadow of dye When a shadow of dye is present, the calcium stones appear as denser spots and the cholesterol stones as translucent defects, often with the characteristic, faceted outline Frequently gallstones are apparent only in the third set of roentgenograms, in which the gallbladder has been partially emptied by the fatty meal Scarcely more than 50 per cent of gallstones can be identified as such, but in the

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cylindruria especially in older individuals Glycosuria is uncommon, and urobilinuria is not particularly significant unless jaundice is present In the presence of hepatitis or when the common duct is occluded, the urine may be stained with bile A serum bilirubin level of from 4 to 6 mg probably is required before bile pigment can pass the renal threshold, so that bile containing urine is not of much value in detecting the milder grade of latent icterus

Examination of Blood — Secondary anemia is uncommon in cholecystic disease but it may follow repeated episodes of jaundice, or it may be associated with the malnutrition which is secondary to long periods of inadequate intake of food Rarely it may follow gastrointestinal bleeding in the exceptional instances in which this is produced by cholecystic disease An examination of the blood smears may reveal a microcytic anemia and thus suggest that hemolytic icterus has been the precursor of gallstones Leukocytosis following biliary colic and in subacute cholecystic disease has been mentioned Because of the fact that not more than 50 per cent of patients with these ailments have significant leukocytosis this finding is not of particular diagnostic value A determination of the sedimentation rate of erythrocytes may indicate the presence of infection but there are so many factors in disease of the biliary tract which alter it that the test cannot be relied on

The *chemical pattern of the blood* rarely is altered Severe vomiting in association with impacted stones in the cystic or common duct will tend to produce an elevation of blood urea and a diminution in plasma chlorides Renal insufficiency with moderate elevations of blood urea and non protein nitrogen and retention of sulphates is not an uncommon occurrence in the presence of obstructive jaundice produced by stones and it is noted quite commonly after choledochostomy Judd and Priestley[90] have noted that renal death' is not a particularly uncommon termination of severe or neglected cholecystic disease Ordinarily renal insufficiency either preoperative or postoperative is not severe and disappears when adequate amounts of fluids are administered

Gastric Analysis — Achlorhydria or gastric subacidity has been cited for years as a frequent accompaniment of disease of the gallbladder Hurst[19] stated that about 25 per cent of patients with cholecystitis and 50 per cent of those with stones show a reduction in the capacity of the gastric mucosa to secrete hydrochloric acid The cause of this phenomenon has never been explained fully and its authenticity is now being questioned It is likely that decreases in acidity if present are of reflex origin and that the use of histamine as a stimulus to gastric secretion would alter these figures considerably When the subject of gastric acidity is studied by statistical means taking into account the normal large incidence of achlorhydria and subacidity, as Vanzant

and her coworkers[148] have done it appears that the acid content of gastric juice is not greatly altered either by disease of the gallbladder or by cholecystectomy, most of the recorded variations being within the range of normal when age and sex are taken into account In the opinion of most investigators the finding of gastric subacidity or anacidity has no diagnostic importance it may however be of some significance in respect to the treatment of the associated digestive symptoms

The use of the duodenal tube to facilitate the diagnosis and treatment of cholecystic disease has had many enthusiastic advocates During the era when it was believed that the gallbladder had no power to empty itself such claims were not generally accepted but now that physiologists[149 150] have shown that evacuation of the gallbladder does occur when magnesium sulphate or olive oil is introduced into the duodenum there has been considerable emphasis on the diagnostic value of this procedure In the hands of enthusiasts who have had a large experience with duodenal intubation and who have been especially interested in the microscopic study of bile the method is undoubtedly of some value however the casual worker who does only an occasional duodenal intubation probably would be more likely to be confused by the findings than to be helped

For a full presentation of the subject the reader is referred to Lyon s monograph[151] and to recent articles by Piersol Bockus and their associates[1 153] Some points of diagnostic value which have been described are (1) failure to obtain gallbladder bile the so-called B fraction on repeated aspirations (2) the demonstration of blood or pus in considerable quantities (3) the presence of pathogenic microorganisms as shown by direct smear or culture and (4) the finding of either cholesterol or calcium bilirubinate crystals In view of the observations of Rous and his associates[119] which have been mentioned previously the finding of pigment of the latter type probably is important a point with which Jones[154] agrees Piersol and his collaborators[1] claimed that stone can be diagnosed more often by duodenal intubation than by cholecystography and also that the functional state of the gallbladder can be correctly diagnosed with greater frequency by this means They concluded that study of the duodenal contents is of more diagnostic value than any other laboratory method a claim which will be disputed by many

Hepatic functional studies in cholecystic disease have had a considerable vogue because of the well known association of hepatic lesions with those in the gallbladder In general the information obtained has been disappointing When frank jaundice is present one can safely assume that hepatic parenchymal damage has occurred a fact which may be corroborated in the more advanced cases by appropriate hepatic functional tests galactose hippuric acid Graham[155] has used tetraiodophenolphthalein for cholecystographic purposes

and at the same time determined the rate of excretion of this dye from the blood, the latter factor being regarded as of some significance in determining the excretory function of the liver He has obtained positive tests in the presence of stone in the common duct and other conditions in which the bile ducts and hepatic parenchyma were infected The ordinary hepatic functional test with bromsulphalein gives similar information

It is not uncommon to have a moderate amount of retention of dye after an episode of acute cholecystitis Cantarow[19] recently has noted that a high percentage of patients with cholecystic disease have some impairment of hepatic function as measured by the bromsulphalein test and by minor degrees of bilirubinemia The problem is to find a hepatic functional test sufficiently sensitive to indicate the minor grades of damage, and yet one which is sufficiently specific so that false positive results are not obtained, such a test has not as yet been devised

Differential Diagnosis

Acute Cholecystitis

The diagnosis of acute cholecystitis may be relatively easy in typical cases, but the absence of any constant relation between the seriousness of the pathologic findings and the severity of the symptoms makes anatomically accurate diagnosis a difficult if not an impossible matter Many experienced surgeons have emphasized the fact that advanced grades of inflammation may exist in the presence of minimal clinical signs and symptoms, and it is equally true that rather striking acute symptoms may be produced by relatively minor lesions in the gallbladder

There are no set rules by which the extent of the inflammatory process may be gauged one must be guided usually by the severity of the local and systemic reactions since pain is an unreliable index In the presence of a palpable and highly sensitive gallbladder slight jaundice fever and leukocytosis diagnosis of calculous cholecystitis may be easy When the pain is diffuse, the local signs of inflammation are slight and when the systemic reaction is not particularly striking it may be difficult to relate the symptoms to the biliary tract.

In actual practice the principal problems are (1) to eliminate the possibility of a perforating or deeply penetrating peptic ulcer (2) to rule out other causes of acute surgical disease of the abdomen such as appendicitis pancreatitis, or occlusion of mesenteric vessels and (3) to exclude coronary infarction In each case the patient should be questioned carefully in regard to previous attacks of pain since the antecedent history may give the clue to the nature

of the attack in question A previous history of ulcer a shock like state the presence of board like rigidity of the abdominal muscles the obliteration of hepatic dulness or the roentgenologic demonstration of air in the peritoneal cavity may be of value in detecting the presence of a perforated peptic ulcer A high lying retrocecal appendix may simulate acute cholecystitis pancreatitis enters into the picture of acute or subacute cholecystitis often enough so that differential diagnosis can hardly be made Parenchymatous hepatic disease is rarely confused with acute cholecystitis but following the recent Chicago outbreak of amebiasis cases of amebic hepatitis with or without the formation of abscess were seen in which the symptoms bore striking resemblance to those of acute cholecystic disease Hepatic syphilis not infrequently is confused with subacute cholecystitis because of the pain fever jaundice and hepatic enlargement which so frequently are associated with specific hepatic disease of this type The almost invariable occurrence of a strongly positive Wassermann test in cases of hepatic syphilis is a diagnostic point of great value Acute coronary infarction often is a difficult condition to exclude The observed association of coronary arterial disease and cholelithiasis has been recognized for years each condition may simulate the other and both may exist in the same case

Faulkner and his collaborators[16] have made a careful comparison of the symptoms of the two diseases and a somewhat similar series of cases has been reviewed by Barker and his associates[17] Among the more important distinguishing features which may be noted are the different sex incidence of the two diseases the antecedent history and differences in the radiation of pain Pain in cholecystic disease rarely radiates to the arms whereas that of coronary disease seldom has the typical posterior radiation so characteristic of pain arising in or about an inflamed gallbladder A falling blood pressure signs of circulatory failure or pericardial friction sounds may settle the matter and since often there is no urgency about surgical intervention in acute cholecystitis time is available for electrocardiographic study which in many instances will identify and locate myocardial infarction

Chronic Calculous and Noncalculous Cholecystitis

The diagnosis of cholecystic disease depends, as is true for most gastrointestinal disorders primarily on an adequate history The old practice of waiting for a major catastrophe such as the development of obstructive jaundice or the formation of an external biliary fistula, has been supplanted by diagnostic methods of considerably greater refinement but without changing the principal requisite a good account of the patient s symptoms While there may be some question of what constitutes a typical gallbladder history

there are many patients whose complaint is sufficiently clean cut to make a diagnosis with a minimum of assistance from laboratory sources The principal inquiries should be directed toward (1) the character, situation and severity of any acute attacks of pain which the patient may have had, (2) the sequelæ if any of such attacks and (3) an appraisal of the flatulent dyspepsia so frequently present Patients often will deny biliary colic but will admit previous attacks which have been diagnosed as 'acute indigestion' or 'gastric neuralgia' Some patients with chronic indigestion alone are prone to exaggerate the severity of their distress and it may require great skill to elicit an accurate and trustworthy account of their symptoms and particularly of episodes of pain connected with them A consideration of the patient's nervous and psychic make up is of value in this connection, in many unstable costive, or migrainous individuals the complaint of pain, if present, must be discounted somewhat. The patient's occupational status eating habits and the qualitative and quantitative relation of food to his distress should be ascertained Finally, in view of the imposing list of other abdominal and systemic diseases which mimic cholecystitis or are associated with it, the history of any additional symptoms or complaints should be reviewed separately Many a history, which at first hearing has suggested the presence of cholecystic disease has by a more expert cross-examiner been found to be clearly related to some other organ

The importance of an adequate general physical examination and the ordinary routine laboratory tests while not particularly significant in any chronic type of cholecystic disease, may be of great assistance in excluding the presence of other conditions liable to be confused with it The value of cholecystography has been mentioned already, but the examination of the patient should not stop with a positive cholecystogram unless the history is quite clearly that of an affection of the biliary tract and that alone The use of duodenal intubation in the diagnosis of doubtful cases is largely a matter of personal preference It is not unlikely that in the hands of experts a limited number of cases of cholecystic disease may be diagnosed by this means alone, even when other methods fail Roentgenograms of the kidneys ureters and bladder taken at the time of the original cholecystogram may enable the physician to avoid making many serious errors on more than one occasion renal stones have produced a good imitation of biliary colic and not infrequently renal and cholecystic stones are found in the same individual Whenever possible a roentgenographic study of the digestive tract should be included in the examination of a patient suspected of having cholecystic disease a peptic ulcer or a cancer of the stomach or colon may be found A diaphragmatic hernia may be detected in this manner it is remarkable how closely a hernia of this type may mimic cholecystitis

In a consideration of the differential diagnosis only the more common sources of confusion and error will be considered Lesions of the stomach and duodenum are a frequent source of difficulty While a majority of patients with peptic ulcer will on questioning admit to a fairly definite sequence of pain in relation to the taking of food there are many whose dyspepsia may be atypical in this and other respects Thus penetrating duodenal ulcers may be responsible for acute attacks of abdominal distress which often mimic very closely pain arising in the biliary tract A cholecystogram followed by roentgenographic examination of the duodenum will settle the question in many cases other patients require prolonged observation on ulcer management As Hurst[36] has pointed out ulcer like dyspepsia in cholecystic disease is not infrequent having as its principal differential diagnostic feature a poor response to ulcer therapy The frequent association of peptic ulcer with cholecystic disease is discussed under another heading and it suffices to say here that it may be very difficult to separate the symptoms of the two diseases when they coexist

Lesions of the upper part of the urinary tract may produce symptoms suggestive of disease of the gallbladder both in the matter of acute colic and in that of chronic indigestion acute attacks of colic like distress may be secondary to renal stone or hydronephrosis and a kidney which is the site of chronic infection or of stones may produce reflex digestive disturbances of *considerable severity In case of doubt an intravenous urogram or retrograde* pyelogram will settle the matter Such a procedure always is advisable if negative cholecystograms are obtained in cases in which patients complain of severe colicky attacks

Disease of the liver likewise presents some diagnostic difficulty particularly in individuals with an enlarged and tender liver and mild degrees of jaundice Because of the reduced excretory function of the liver in these cases cholecystographic evidence of a non functioning gallbladder may be obtained also gallstones are not an uncommon late development in cases of chronic hepatitis of various types In such cases hepatic functional tests may give information of value but sometimes exploratory laparotomy is required to settle the diagnosis The abdominal crises of plumbism and of tabes dorsalis have been mistaken for biliary colic the occupational history the demonstration of a lead line on the gums signs of encephalopathy and anemia with basophilic stippling should serve to identify plumbism The presence of considerable quantities of lead in the urine is also a feature in these cases The exclusion of tabes dorsalis *appears to be a more difficult problem if one may judge by the* number of patients who have undergone cholecystectomy before a correct diagnosis has been made The associated neurologic signs of tabes should be sought for in every case in which there is acute abdominal pain and vomiting

and when these are at all questionable serologic examination of the blood and spinal fluid will, in most instances, serve to identify the condition Even when the syphilitic process in the nervous system has largely burned out and the serologic tests are negative, the diagnosis can be made on the basis of neurologic findings and on the character of the attack The diffuseness of the pain in tabetic crisis, the zones of hyperesthesia, the character of the pupils and the absence of deep reflexes in most instances should lead to a correct diagnosis

Hemolytic icterus often is confused with cholecystic disease because of the fact that definite abdominal distress and tenderness frequently are present during crises of erythrocyte destruction and jaundice What makes the problem still more difficult is the fact that hemolytic icterus, when of long duration is associated with gallstones in approximately 60 per cent of cases The family history, if obtainable, often is helpful, and a palpable spleen should of itself attract attention to the possibility of a blood dyscrasia An examination of the blood smears which should show microcytosis and a high reticulocyte count an elevated serum bilirubin with indirect van den Bergh reaction and a demonstration of reduced fragility of the erythrocytes should be of great assistance in arriving at a correct diagnosis

Lesions of the appendix and cecum are common causes of error Chronic or subacute appendicitis is associated so frequently with cholecystitis that its presence should be considered in every case It is not uncommon for the appendix to be removed and the diseased gallbladder to be left behind Malignant lesions of the cecum cause less difficulty they are as a rule, associated with diarrhea and marked secondary anemia both of which are rare in cholecystic disease Most lesions of the cecum also produce some rather acute changes in the intestinal habits of the individual, which in turn would indicate the necessity for roentgenologic examination of the colon and lead to a correct diagnosis

Gastrointestinal allergy also may be a source of difficulty, since the distress which may follow an allergic seizure in an affected individual may, at times be severe There may be mild chronic digestive disturbances also which are referable to the ingestion of substances to which the patient is only mildly sensitive It is of importance in this connection to note that *Deissler and Higgins*[1 8] recently have shown that the gallbladder itself may contract powerfully in response to the stimulus of an allergin This further complicates the problem and puts under suspicion the rather large group of allergic individuals who have symptoms which mimic disease of the gallbladder An inquiry into allergic factors becomes, therefore an important part in the taking of the history A number of cases have been reported[1 9] in which what appeared to be gallstone colic was not relieved by the removal of a normal appearing gallbladder, and the symptoms disappeared after the removal from the diet of a few foods

Among the less common ailments, which because of the pain they produce simulate cholecystic disease one must consider the residual pain of herpes zoster the root pain of tumors of the spinal cord irritation of the nerve roots from arthritis of the lower thoracic spine or from Pott s disease in this region, pain caused by the pressure of aneurysm of the descending aorta various types of pleurisy, especially pyogenic or tuberculous types and diaphragmatic hernia

In all of the conditions mentioned in this consideration of the differential diagnosis there is a reasonable probability of arriving at a correct conclusion and errors in the field should not be numerous Brown[160] estimates the maximal accuracy of diagnosis at about 90 per cent The most difficult diagnostic problems are presented by two groups of patients namely (1) those with an irritable gastrointestinal tract spastic constipation pylorospasm and migraine singly or in combination and whose gallbladders produce faint shadows after the administration of dye and (2) nervous or hypersensitive patients who have attacks of upper abdominal pain resembling biliary colic and who have been said to have pseudo-cholecystitis In such cases cholecystectomy may be curative but all too frequently it is performed without the slightest benefit. There is no diagnostic procedure which will settle the matter but surgeons have learned to be extremely wary of operating on the biliary tract when there is no definite history of colic and a conservative course rarely will be regretted If possible radical treatment should be deferred until there is some indisputable objective evidence of disease of the biliary tract

Cholecystitis Associated with Other Diseases

The association of disease of the gallbladder with that of other organs rests to a great extent on clinical impressions rather than on statistical proof When one makes an accurate statistical study of a series of postmortem examinations as Maisel and Alvarez[161] have done the supposed significance of some of these coincidences diminishes considerably because of the frequent coincidence of cholecystitis with the commoner abdominal disorders and also with the degenerative diseases which form so large a part of the ailments of the fifth and sixth decades of life For instance diabetes mellitus always associated in the minds of physicians with cholecystitis and cholelithiasis cannot be shown to exist with much more than average frequency in cases of cholecystic disease[162], the association of the two conditions probably is attributable to the fact that both diseases are common in obese middle aged individuals. Most of the reported associations between cholecystic lesions and disease in other organs is of little statistical value for two reasons there has been no standard basis for determining what constitutes disease of the gallbladder and

the other organs in question, and there has been no adequate study of a control group of equal size and of the same general distribution in respect to age sex and environmental status The discrepancies between clinical impressions and real statistical correlation are particularly clear in the case of heart disease

It is common to encounter patients with known calculous cholecystic disease who complain of abnormal consciousness of the heart s action, anginoid pains or, in rare instances, actual failure of cardiac competence In the older literature there are many reports of observations on improvement in cardiac function after cholecystectomy and in fact this type of case has been dignified by the term cholecystic heart It is not particularly uncommon to see milder types of cardiac complaint of this general nature completely relieved by cholecystectomy, and even with more severe cardiac damage improvement may follow operation Willius and Fitzpatrick[163] found that 39 per cent of a group of patients with chronic cholecystic disease had definite changes in the cardiovascular system, of which hypertensive heart disease and coronary sclerosis were the most common Seventy nine of the group with organic disease of the cardiovascular apparatus were subjected to cholecystectomy There was only one postoperative death from cardiac causes and 54 per cent of the group were definitely improved with regard to the cardiac symptoms Schwartz and Herman[164] noted an incidence of cardiovascular disease amounting to 63 per cent in a group of patients with cholecystitis, with or without stones in a control group from the wards of the same hospital from which patients with rheumatic fever and cholecystitis were excluded only 41 per cent had cardiovascular lesions *Leech*[165], *however* reported another clinical study in which there was no correlation between diseases of the biliary tract and the heart and Maisel and Alvarez[161] likewise found a negative correlation between the two conditions in a series of 1 384 postmortem examinations Gross[39] has shown a statistical relation between gallstones and atheroma and a questionable relation between stones and nephritis which may have been due in part to the age groups studied It is difficult to prove from the available material that cholecystic disease and cardiac disease are in any way related as far as actual gross lesions are concerned and even if such a correlation existed the fact remains that both lesions may have originated from a common cause The work of Buchbinder[166] and Owen[167] seems to indicate that the production of cardiac symptoms by cholecystic disease is largely due to increased irritability of the cardiac mechanism from which it may be implied that the cardiac disturbances encountered in clinical cholecystitis are caused by reflex nervous phenomena or toxic influences.

Of the common abdominal diseases, chronic appendicitis chronic hepatitis and pancreatitis can be shown to be statistically related to cholecystic disease

a point with which clinicians and surgeons generally will agree There does not seem to be any definite association with gastric and duodenal ulcer[39, 161] although the two conditions are frequently seen in the same individual There is no relation to pelvic disease in the female but some correlation with prostatic disease has been observed

The relation to joint diseases, neuromuscular pains and so forth has been stressed by some writers but no statistical studies are available to confirm this impression In the age groups represented one would expect a fairly high incidence of senescent and metabolic types of joint disturbance one also must consider that in the obese individual who is always well represented in any collection of cases of cholecystic disease there is a considerable amount of static disturbance in weight bearing joints Judd and Hench[168] found that the gallbladder did not often act as a focus in arthritis and that its removal was followed by improvement in only a minority of cases

There is no relation between cancer and cholelithiasis but all authorities agree on the very high incidence of gallstones in connection with malignancy in the gallbladder and bile ducts Gross[39] noted that this association concerns only the faceted or common gallstones and that it does not apply to cholesterin stones.

Prognosis of Benign Cholecystic Disease

The prognosis in the various forms of benign cholecystic disease is difficult to make as must be apparent from the foregoing discussion In the majority of cases the lesion which ultimately brings the patient to a physician is of long standing and represents the end stage of repeated infectious or metabolic disturbances Long histories are the rule it is not difficult to find individuals with complaints referable to the gallbladder of twenty or more years duration. The danger to life of chronic cholecystic disease probably is not great and most patients appear to tolerate the condition fairly well as Blackford and his colleagues[169] have shown in their review of a series treated medically

However many of these individuals whose disease pursues a relatively mild course may encounter serious difficulties in the later years of their lives Perhaps the best idea of the potential danger of neglected cholecystic disease can be obtained from reading the literature of the period which preceded the modern surgical treatment of lesions of the gallbladder it is replete with accounts of complications and catastrophies of every description seldom encountered in modern practice It is the remembrance of these things which doubtless must weigh heavily in the opinions of some older surgeons who believe that immediate cholecystectomy is to be urged on every patient who is diagnosed as having cholecystic disease

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The outlook for acute or subacute, noncalculous cholecystitis is good, so far as the immediate attack is concerned, if one excludes typhoidal cholecystitis, which is now very rare, perforation or other serious consequences are uncommon Acute calculous cholecystitis associated with cholangeitis and hepatitis may pursue a less favorable course and certainly presents a more serious problem, if the attack in question does not require immediate operation, which incidentally involves an increased surgical risk, the gallbladder is left with inflammatory changes in its walls which favor further infection and the formation of stone A single severe attack of acute cholecystitis should, under most conditions be followed by radical surgical treatment

The prognosis in cases of chronic and apparently noncalculous cholecystitis depends on so many factors in the individual case that no satisfactory general rule can be laid down The affected individual can, in the milder cases, look forward to nothing worse than chronic dyspepsia Less frequently he may become the victim of a progressive and disabling disease The difficulty in prognosis lies in the fact that one can seldom be sure that stones are not present nothing short of surgical exploration can settle that question definitely With mild symptoms and no evidence of progression the patient's interests are not prejudiced by following a conservative course, if pain is severe and attacks are coming frequently there is little advantage in postponing operation The social and environmental status of the individual, the psychic make up and the presence or absence of disease in other organs affect the prognosis in supposed chronic cholecystitis one becomes extremely cautious about holding out promises to the psychically unstable individual, since in such cases neither surgical nor medical treatment yields satisfactory results.

If stones are found accidentally at operation on other abdominal organs, or if they can be demonstrated in the cholecystogram there is a good chance of subsequent trouble even if there have never been any symptoms referable to the gallbladder, it is remarkable how frequently one sees older patients who, after an occasional biliary colic in earlier life are admitted to the hospital with an obstruction of the common duct due to stone or with gangrenous cholecystitis However, it is almost as common to discover totally unsuspected stones at necropsy

Most surgeons look on stones as pregnant with possibilities of evil and certainly if a patient with cholelithiasis proved by roentgenologic examination, has enough digestive disturbances to seek medical attention he can be assured that his future is not secure and that there is always the possibility that cholecystectomy eventually will be necessary An exception may perhaps be made in the case of cholesterin "solitaires which at least, cannot get into the common duct and which are not as a rule associated with active cholecystitis In general the prognosis in the presence of cholelithiasis is dubious and the

patient may prefer to have cholecystectomy performed at a small risk rather than to await some of the more serious and dangerous complications of stones in later life

Without reference to morbidity stones constitute a definite menace to life There is some statistical evidence to suggest that patients with cholecystitis whether or not stones are present have a reduced life expectancy and that their chances of survival are improved after cholecystectomy at least life insurance companies appear to base their calculations on this probability

Dublin and his collaborators[170] *recently have reported that the mortality* experience of the Metropolitan Life Insurance Company was somewhat higher than normal for a group of nearly 3 000 individuals who had a history of disease of the gallbladder whether operations on the biliary passages had been performed or not The women in the group had an approximately normal mortality but among the men the mortality was 126 per cent of that which would have been expected in individuals of the same age In male patients the experience following cholecystostomy was particularly unfavorable but this operation had no significant effect on the average mortality among the women The length of the interval between illness or operation and the time insurance was granted did not seem to be an important factor and the high death rate was distributed quite evenly among the different age groups A rather high percentage of deaths in the whole group was attributed to malignant and non malignant *disease of the digestive tract the high cancer rate being* limited almost entirely to the males

TREATMENT OF BENIGN CHOLECYSTIC DISEASE

Non Surgical Treatment

Acute Cholecystitis —The treatment of acute cholecystitis ordinarily is expectant, since most acute lesions of the gallbladder subside without perforation A light diet an ample intake of fluid and an ice pack to the gallbladder are the principal requirements in the average case Morphine is of course *necessary to* control the pain

The use of small doses of magnesium sulphate to relax the sphincter of Oddi which may be in spastic contraction has been recommended Atropine or its derivatives may be helpful in producing some inhibition of contraction Duodenal intubation, as practiced by Lyon[11] depends on this same principle and may be of service in the subacute case Hurst[171] has recommended hexa methylenamine to disinfect the gallbladder but there is some doubt as to the efficacy of this method The dye commonly used in cholecystography tetra iodophthalein has a proved bacteriostatic effect and occasionally a patient will claim to be much better for a time following cholecystography

The ultimate treatment of acute or subacute cholecystitis is, of course, surgical and the principal problem is that of selection of a time for surgical interference Competent authorities argue that because of the uncertainty of diagnosis the danger of any acute inflammatory process within the abdomen, the frequent lack of agreement between the severity of the clinical symptoms and the degree of disease of the gallbladder, early exploration is advisable Recent publications by Stone and Owings[172], Smith[1 3], Judd and Phillips[4] discuss the problem in more detail than is possible here In general, today, there is less fear of immediate surgical intervention than was formerly the case There are many instances in which surgical treatment may safely be postponed, however and there is no satisfactory plan which is applicable to all cases

Chronic Cholecystic Disease — Medical treatment can hardly be counted on to work a real cure in the presence of the more severe grades of cholecystitis when individuals suffer from repeated biliary colic or when the gallbladder is the site of an active infectious process There are however a considerable number of cases of cholecystitis in which the diagnosis is made fairly early in the course of the disease and in which the symptoms are minimal, and the indications for surgical treatment are not clear Patients with this type of disease may receive the benefit of medical treatment such as it is Even in more severe cases it is often necessary to defer a needed operation for economic or other reasons and under these circumstances some type of medical management may be advised in the hope of procuring temporary symptomatic relief Postoperative medical treatment is also of importance in cases in which there is a residuum of digestive disturbances following operation

Medical treatment consists chiefly of regulation of the diet, the use of drugs which favor evacuation of the gallbladder and which may serve to sterilize the biliary passages and possibly such special methods of treatment as duodenal drainage A great many conflicting opinions have been advanced with regard to the dietary measures in general Some would go so far as to say that there is no logical diet or treatment for cholecystitis and they can demolish the argument of anyone who cares to tilt with them The fact that ingested fat leads to the production of cholecystokinin and thus causes evacuation of the gallbladder makes it appear advisable that patients be given an adequate intake of fat The gallbladder of the asthenic or underweight individual with cholecystic disease may be atonic, and in such cases a high intake of fat may not only improve the general nutrition of the individual, but may also favor the normal evacuation of the affected organ In obese individuals a low intake of fat is desirable chiefly as a means of reducing weight, if the gallbladder is of the irritable or hypermotile type the ingestion of fat will increase the patient s distress and may be contraindicated for that reason In general therefore, the tolerance of patients to fat can best be determined by trial and

error The value of a diet with a low content of cholesterol has been emphasized by many observers but as a rule this is simply making the mistake of locking the barn door after the horse is stolen While the relation of cholesterol metabolism to cholecystic disease in general and to the formation of stone in particular is not as yet conclusively proved it seems reasonable to suppose that a reduced dietary intake of cholesterol may be of some value in avoiding the further deposition of cholesterol in the wall of the gallbladder or its precipitation from the bile Egg yolk is the principal source of cholesterol in the diet Butter contains moderate amounts and kidney liver sweetbread and brain also are high in cholesterol content Various types of diets low[1 4] in cholesterol have been outlined for use in the medical treatment of cholecystitis and they may be worth a trial particularly in obese individuals

In general whatever diet is prescribed should be of a bland and non irritating type because of the reflex gastrointestinal disturbances which are such common accompaniments of cholecystic disease What is really needed is a type of diet to relieve the flatulent dyspepsia but unfortunately this has never been devised The obese patient should be urged to reduce his diet and the asthenic individual should be advised to improve his nutrition but otherwise dietary treatment seems to offer little of value

Drugs which have been used in the treatment of ailments of the gallbladder may be classified as (1) those which relax the sphincter of the common duct and thus favor evacuation of the gallbladder (2) those which are intended to sterilize the bile passages and (3) those which increase the flow of bile A fourth group includes drugs which are employed for their sedative effect on the gastrointestinal tract Olive oil which has been recommend d for years is useful in relieving cholecystic dyspepsia especially when taken before meals it not only inhibits gastric spasm but may also serve to relax the sphincter of Oddi It is not well tolerated in the presence of gastric anacidity Small doses of magnesium sulphate may be given before breakfast for the relaxing effect on the sphincter and with the idea of draining the gallbladder some authorities feel that it is fully as effective when used in this way as when given by duodenal intubation If draining were the main desire egg yolk and cream should be given as it gives more marked emptying than magnesium sulphate Sodium phosphate before meals may also relieve dyspepsia for reasons which are not entirely clear Atropine or its derivatives when given to the point of physiologic effect is supposed to be of particular value in the presence of associated pylorospasm or when the gallbladder is hypermotile and spastic It may be used advantageously with sedatives either bromides or barbiturates Drugs which cause contraction of the gallbladder such as pilocarpine and pituitrin are rarely used Cholecystokinin must also be mentioned in this connection it has not been used in clinical cases

Sodium dehydrocholate or 'decholin' has been used for its effect in increasing the flow of bile, and because of the high content of bile salt, which should follow its use it may tend to keep cholesterol in solution if this is desirable The clinical results have been disappointing Under ordinary conditions there is little reason for the use of cholagogues in cholecystic disease, the common patent remedies, which consist of compounds of laxatives and bile salts appear to be of more value from a psychic than from a physical standpoint In fact there is no good reason for their use except that patients feel that they must do something

There are certain patients with cholecystic disease and hyperchlorhydria who have digestive disturbances which closely simulate those of ulcer Such patients may be benefited by a modified type of ulcer management and by the use of alkaline powders and antispasmodics An occasional patient with *gastric anacidity and associated indigestion may receive benefit from the use* of dilute hydrochloric acid in full doses

Numerous attempts have been made to sterilize the bile passages by chemical means Mercurochrome has been used for this purpose, but since the composition is altered by passage through the liver it has little bactericidal effect in the bile Salicylates have been recommended for their cholagogic effect and for their supposed antiseptic action on the bile Hurst[1 1] advised the use of hexamethylenamine in massive doses in conjunction with alkalies The use of the drug in this fashion is based on the observations of Knott[17], who has claimed that urotropine (hexamethlenamine) is antiseptic in bile in spite of the alkaline reaction of the latter Hurst[171] advised a large dose of urotropine (hexamethylenamine), 100 grains (6 5 gm) with 60 grains (4 0 gm) each of sodium citrate and sodium bicarbonate twice daily, the urine being examined at regular intervals to be certain that hematuria is not produced Ottenberg[176] in an experimental study of biliary antiseptics has noted that flumerin (disodium 2 hydroxymercurifluorescin) also rendered the bile bactericidal for typhoid bacilli and other organisms but no clinical study with the use of this substance has been reported In general it may be said that the use of biliary antiseptics is somewhat irrational because of the well known fact that in cholecystitis the wall of the gallbladder rather than the bile is affected The removal of foci of infection while theoretically of value, seems to be of little effect in the course of cholecystic disease and the same may be said as to the use of autogenous vaccines

In general medical measures in the treatment of cholecystic disease should be confined to the use of a bland diet with a fat content adjusted to the needs of the individual patient the use of drugs which tend to relax the sphincter of the common duct and favor evacuation of the gallbladder and any additional symptomatic remedies which will tend to relieve the associated dyspepsia

Special types of treatment, such as repeated nonsurgical drainage of the gall bladder by means of the duodenal tube may be helpful in cases in which patients can afford the time and expense In the milder degrees of cholecystitis and for patients with so-called biliary dyskinesia or stasis gallbladder this form of treatment may be of some value Lyon[177] has been particularly enthusiastic about the therapeutic advantages of this method but gastroenterologists in general have been somewhat skeptical and most surgeons openly antagonistic Spa treatment is of course out of the question for a large majority of patients but it is still popular among the affluent The alkaline waters of Vichy and Carlsbad are said to reduce the hypercholesterolemia occasionally associated with gallstones In general the benefits of this type of therapy are doubtful although the rest purgation and reduction of weight commonly attained at such resorts may be temporarily beneficial

Surgical Treatment

Surgical Indications — While the surgical indications are more properly considered in surgical texts the general rules for the selection of cases for cholecystectomy have become common property[1 8] There are certain indications for surgical treatment which are quite generally agreed upon (1) repeated attacks of biliary colic or of acute cholecystitis with or without jaundice or fever regardless of the cholecystographic findings (2) a permanently distended and palpable gallbladder (3) the association of other abdominal diseases such as peptic ulcer or appendicitis in an active form (4) persistent and severe digestive disturbances which are not adequately controlled by medical means and (5) signs of infection or hepatic damage in cases in which patients are known to have gallstones There are other groups of cases in which the surgical indications are not so clear These include (1) patients with a normally or poorly functioning gallbladder as shown by cholecystography who have mild qualitative and quantitative food distress and abortive or mild biliary colic (2) neurasthenic individuals with vague digestive disorders and roentgenologic evidence of disease of the gallbladder with or without visible stones (3) patients with a solitary cholesterin stone who have minimal symptoms and (4) individuals whose complaints probably are due to motor disturbances in evacuation of the gallbladder biliary dyskinesia The clinical identification of the condition in this last group is admittedly difficult but eventually it may be possible All of these doubtful cases eventually may require surgical treatment but in the main one is justified in attempting conservative treatment until more definite symptoms appear

It has been observed repeatedly that in cases in which patients have not had biliary colic the results of surgical treatment are distinctly inferior to

those obtained when the patients have had severe pain Cholecystographic findings cannot and should not be relied on absolutely to furnish surgical indications For example, one may cite the faintness or absence of the cholecystic shadow in cases in which patients present conditions of lowered metabolism the so-called atypical hypothyroidism In such cases elevation of the metabolic rate will relieve symptoms in a considerable percentage, and the shadow of the gallbladder will resume its normal density Primary hepatic disease will give similar cholecystographic findings and its presence should always be considered in doubtful cases On the other hand, a gallbladder which fills and empties normally and shows no important change on roentgenologic examination may contain stones and a negative cholecystogram in the presence of an adequate history of colic does not mean that surgery should not be considered

In general cholecystectomy is the operation of choice, cholecystostomy being performed usually because of local technical difficulties the poor condition of the patient or the presence of doubtful or threatened obstructive lesions of the common duct when it may be advisable to save the gallbladder for subsequent anastomosis to the stomach or duodenum Some experienced surgeons perform cholecystostomy in the presence of acute infections of the liver and bile passages however unless the gallbladder is removed the patient is left with a definite focus of infection in the cholecystic wall, and it is doubtful if a gallbladder which has been subjected to surgical drainage, ever functions in an entirely normal manner thereafter[179] Stones may, and frequently do, reform in such gallbladders and digestive disturbances are likely to persist

The recent review of Judd and Priestley[90] indicates clearly the disadvantages of cholecystostomy and the tendency for a large percentage of patients, who have had this operation to have further trouble In clinical practice one sees many patients who have undergone cholecystostomy for various vague types of indigestion and who have continued to have the same symptoms which existed prior to operation In this group subsequent cholecystectomy seldom has a favorable effect and should not as a rule be advised unless there are frank colics, or unless stones can be demonstrated by cholecystography

End Results — The general results of cholecystectomy for disease of the gallbladder are surprisingly good On several occasions extensive inquiries into the health of patients after operation have been made by surgeons at the Mayo Clinic and elsewhere and good results have been recorded in from 65 to 90 per cent of all cases in which the patients could be traced Patients, whose gallbladders were the site of severe infective cholecystitis or marked cholesterosis with stones have the highest percentage of good results For those with various lesser degrees of cholesterosis the outcome was distinctly less favorable unless definite biliary colic had been a feature of the case Graham and Mac

key[89] recently have emphasized the rather uncertain results obtained by removal of noncalculous gallbladders and they noted that about 40 per cent of such patients had continued postoperative complaints Usually it is found that most patients who have had frank colics regardless of the state of the gall bladder at operation report satisfactory results For individuals with vague symptoms of dyspepsia exhaustion neuromuscular pains and migraine a les satisfactory outcome is the rule

When the results of surgical treatment are unsatisfactory the blame can be laid to four factors[180] (1) erroneous diagnosis and a poor selection of cases for operation ( ) the residues of cholecystic disease such as inflammatory lesions of the liver bile ducts or pancreas (3) the leaving of stones in the common duct, and (4) trauma to the common bile duct at operation

The matter of diagnosis has been considered in an earlier section and the common association of disease in adjacent organs likewise has been discussed Probably at least 20 per cent of the patients who have undergone chole cystectomy are left with some residual damage in the liver pancreas or bile ducts Improvement usually follows cholecystectomy but for obvious reasons instantaneous relief cannot be expected In some cases it never comes The usual symptom of such residual lesions is that of persistent flatulent dyspepsia with variable degrees of pain and tenderness in the right upper quadrant of the abdomen Gaseous indigestion is a frequent complaint and may persist for long periods of time after operation

Colics Following Cholecystectomy —Among the most puzzling ailments following cholecystectomy are the so-called post cholecystectomy colics These include (1) the colics which appear to accompany postoperative distention of the common and hepatic ducts and the resumption of sphincteric tone (2) those which are associated with incomplete cholecystectomy the presence of stone in the common duct hepatitis or cholangeitis and (3) those which are unexplained except on the basis of a spastic sphincter of the common duct and so-called biliary dyskinesia

Postoperative colic occurring in the weeks immediately following chole cystectomy is not infrequent It resembles biliary colic in every detail except that usually it is less severe it is probably related to the slow dilatation of the bile passages which follows cholecystectomy or to increased sphincteric tone These colics may persist for some weeks or months but as a rule they disappear spontaneously within a short time and are of no particular signifi cance Since they are very alarming to the patient some mention of them should be made at the time of dismissal

The symptoms which follow incomplete cholecystectomy usually are delayed in their onset and in general are those of the original lesion in the gallbladder Occasionally there is a history of technical difficulties at the time of operation

with prolonged postoperative drainage of bile or even a biliary fistula, occasionally roentgenographic examination may show a stone in the remaining fragment of gallbladder or in the stump of the cystic duct[181] Stone in the common duct and cholangeitis will be considered in a later section, it should be noted that such stones frequently are overlooked at the time of the original cholecystectomy and unless the duct has been opened and explored one cannot be certain that stones were not present If there were stones in the gallbladder at the original operation the probability of stone in the common duct is increased There may be a long interval of freedom after the original operation, during which the stone probably is increasing in size to a point where it may produce obstruction Cholangeitis ordinarily subsides spontaneously after cholecystectomy especially if the common duct is surgically drained, but there are cases in which re operation and the establishment of drainage may be necessary

Colics which apparently are due to some disturbance of the function of the common duct with spasm of the sphincter, constitute an extremely difficult problem The mechanisms of these attacks have never been satisfactorily explained but it is thought that there is a failure in the nervous mechanism that perhaps causes the sphincter or the common duct itself to assume a state of spastic contraction under certain conditions[15] The colic may be as severe as that which is associated with stones, but it is not accompanied by chills, fever or jaundice Intubation of the duodenum will reveal no evidence of obstruction to the flow of bile, and specimens of bile obtained by this means will show no pathologic sediment of any kind In a number of such cases the common duct has been carefully explored, and no lesion, which would satisfactorily explain the symptoms has been found either in it or in the liver[183, 184] Curiously enough prolonged drainage of the common duct with a T tube relieves many of these individuals but some may have colics even with the tube in place Section of the splanchnic nerves has been attempted and occasional good results have been noted In one case encountered at the Mayo Clinic novocaine ' block ' of the sixth seventh and eighth thoracic nerve roots completely relieved a severe colic but splanchnic section in this same case was without any particular effect Most of the unexplained colics, which have been observed have occurred in neurasthenic women and while there was no reason to believe that these patients were exaggerating their distress it seemed apparent that there was some type of abnormal visceromotor mechanism at work Treatment in these cases has been rather haphazard and unsatisfactory Bland diets antispasmodic drugs and sedatives the use of cholagogues and repeated duodenal intubation occasionally may produce some relief irradiation of the thoracic nerve roots involving the affected regions may be helpful The possible benefits of splanchnic section have not as yet been

evaluated and in the cases in which the pain is severe and persistent recourse has generally been had to the establishment of drainage of the common duct by T tube

Tumors of Gallbladder

Benign Tumors

If one excludes the multiple small papillomas which occur in about 8 to 10 per cent of gallbladders removed surgically, benign tumors of the gallbladder are rare and in fact are considerably less common than carcinoma of that organ The small papillomas frequently are less than 0 5 cm in diameter and their height is about five or six times that of the normal villi They are multiple in about 60 per cent of cases and distributed in a patchy manner throughout the gallbladder[185] Often found in association with cholesterosis they may themselves contain large amounts of cholesterol microscopically they resemble the hypertrophied villi seen in association with cholesterosis and the larger ones may be branched There is some evidence[186] to indicate that portions of the larger papillomas may break off to form the nuclei of gall stones A large percentage of gallbladders with papillomas are also the site of chronic or subacute inflammatory lesions and not infrequently contain stones Thirty per cent of the papillomatous gallbladders in Baumgartner's series contained calculi either single or multiple There is little evidence to indicate that these papillomas ever undergo malignant degeneration Phillips[18] could find only one case out of a series of 500 in which this might have occurred

Larger papillomas are classed with the surgical curiosities They are usually described as extremely friable and soft and they may fill the gall bladder almost completely They have been known to break off and lie free in its lumen These larger papillomas may be stained with bile or encrusted with deposits of bile pigment often they are inflamed or edematous Papillomas of a distinctly myomatous character have also been described It is possible that in some large papillomas malignant changes may eventually develop at least they have been known to spread by extension Abell[187] described a case in which a papilloma formed in the common bile duct following the removal of a large papilloma which completely filled the gallbladder and Henry[188] and Kiraly[189] have had similar experiences The relation of the larger papillomas to the presence of stones is uncertain, but Sand and Mayer[190] found stones in seven of the eight cases which they described

Myomas[1 1] lipomas fibromas myxomas and mixed types of benign tumor have been found in the gallbladder but they are extremely rare Adenomas which may reach considerable size and are sometimes cystic[19] are considerably more common Abell[187] noted 8 3 of which were papillary in 288 cholecys-

tectomies but his experience was probably unusual, since Wellbrock[193] found only 69 adenomas in 9 550 specimens In all but four cases of Wellbrock s series the tumor arose in the fundus, and in 38 of the group stones were found in association with the tumor There are certain rare changes in the wall of the gallbladder which may simulate benign tumor A case of cholecystitis glandularis proliferans described by Wiglesworth[194], is an example Extensive cystic changes in the mucosa of a similar type have been described in chronic cholecystitis without true adenoma formation and intramural calculosis has been reported

Diagnosis of Benign Tumors — The diagnosis of benign tumors is not often possible they produce no characteristic symptoms, the clinical picture associated with them being usually that of chronic cholecystitis Kirklin[195] has reported the diagnosis of papilloma in 51 cases by means of cholecystography the tumors appearing as oval or round defects frequently marginal, in a cholecystic shadow of normal or increased density The unusually dense shadow in these cases may be explained by the studies of Caylor and Bollman[16] who demonstrated that gallbladders with the hypertrophied rugæ, so often associated with papilloma produce a maximal concentration of bile Kirklin[195] has also been able to diagnose adenomas of the gallbladder by the presence of a transradiant hemispherical defect in the cholecystographic shadow usually located at the fundus

Malignant Tumors

Primary Sarcoma of the Gallbladder — Primary sarcomas are extremely rare Rolleston and McNee[196] mentioning only 19 references to such tumors and de Gaetani[197] only 36 Iwasaki (1914)[198] described 8 cases from the earlier literature in all but one of which the sarcoma was associated with stones Carson and Smith in 1915[199] reported the findings of a large round celled sarcoma in a stone containing gallbladder and Judd and Baumgartner[200] recently have described an almost identical case The pathologic findings in the cases reported are variable polymorphous types angiosarcomas myosarcomas endotheliomas and lymphosarcomas have been described In two instances on record the formation of cartilage and bone was noted in the wall of the gallbladder In about two thirds of the cases reported its patients were women of the cancer age The symptoms are essentially identical with those of primary carcinoma of the gallbladder and the differential diagnosis from the latter condition is impossible The prognosis ordinarily is bad since metastasis to adjacent organs, particularly the liver apparently occurs early Cathcart s patient, cited by Goldstein[201], was an exception and survived cholecystectomy for some time

Primary Carcinoma of the Gallbladder — A primary carcinoma of the gall

bladder apparently was encountered much more frequently forty or more years ago than is the case today The largest series of cases reported dates to 1901 W J Mayo in 190 found carcinoma in 5 per cent of a series of 405 operations on the gallbladder, while MacCarty reporting from the same institution seventeen years later noted an incidence only one tenth as great in a series of 5 000 gallbladders removed surgically In 1929 Judd and Baumgartner found only 5 primary carcinomas of the gallbladder in reviewing a series of 1,094 cholecystectomies In other words the incidence of primary cancer of the gallbladder at the Mayo Clinic has declined from 5 per cent to 0 5 per cent in twenty five years These low rates of incidence are confirmed from other sources Deaver and Bortz (19 7) found carcinoma in but 1 5 per cent of their series of 903 cases of cholecystic disease and Lotzin in 1926 reported a 1 per cent incidence of the condition in 943 necropsies So marked a decrease in incidence can best be attributed to the fact that calculous disease of the gallbladder is now diagnosed and treated surgically at an earlier stage than formerly and that fewer stone containing gallbladders the usual site of carcinoma are carried into the later years of life

Carcinoma of the gallbladder however is still by no means rare in clinical practice, and it is said to constitute about 5 per cent of all primary carcinomas found at necropsy The gallbladder ranks fifth among the sites of carcinoma of the digestive tract being preceded by the stomach colon rectum and esophagus in that order Statistics bearing on the incidence of the disease are somewhat difficult to evaluate since a majority of the recently reported series of cases is rather small It is generally agreed that the condition is about three times as common among women as men this is the figure given both in Musser's early series of 100 cases and in more recent reports It is distinctly a disease of older individuals being a great rarity in early life In 74 per cent of the cases in Judd and Baumgartner's series the condition was encountered in patients between the ages of fifty and sixty years

The association of chronic cholecystic disease and cholelithiasis with primary carcinoma is a matter of much interest and one which has been widely quoted in promulgating the theory of chronic local irritation as a cause of cancer The incidence of stones in cancerous gallbladders varies from 48 per cent to 100 per cent in most of the recently reported series the incidence of stones averages not less than 65 per cent The question of whether the stones preceded the development of neoplasm or whether they developed later has been discussed vigorously and still is undecided but most authorities believe that cholelithiasis is the primary lesion Lentze and Siegert found that whereas gallstones were present in 95 per cent of cases of primary carcinoma stones could be demonstrated in only about 15 per cent of secondary carcinomas of the gallbladder These figures have been quoted to prove that stones

are the exciting cause of carcinoma of the organ In the experimental animal Leitch[1] claimed to have produced neoplasms by the introduction of gall stones and pebbles into the gallbladders of guinea pigs His results have been questioned by Delbet and Godard[13] and by Burrows[14], the last named investigator being inclined to the view that, while the presence of stones under these conditions produced rapid proliferation of the mucosa and papillomas, no true cancer developed

Pathology of Carcinoma of Gallbladder —According to Ewing[1] there are three types of gross lesions found (1) a villous, papillomatous or fungating growth, (2) a diffuse, flat and infiltrating type which resembles scirrhous carcinoma, and (3) a gelatinous carcinoma, which infiltrates the wall and fills the cavity of the gallbladder On microscopic examination the picture most frequently encountered is that of adenocarcinoma, squamous cell lesions have been described and since the gallbladder contains no squamous epithelium, these are presumably the result of metaplasia Rarely, both adenocarcinoma and squamous cell types have been found existing in the same gallbladder Rosenthal[16] has noted primary melanocarcinoma The tumors have been said to originate chiefly in the fundus because of the pressure of stones at this point Judd and Gray[17], however found that there was no predilection for any particular point in the cholecystic wall Hour glass contraction has been described in association with growths arising in the infundibulum, those which involve the neck of the gallbladder may produce stricture at this point with subsequent hydrops

The tumor may, and frequently does involve the common duct by compression thus leading to obstructive jaundice compression of the portal vein with subsequent thrombosis has also been described as a terminal event The association of stones and infection of the wall of the gallbladder may easily lead to local abscess formation For this reason ulceration and the formation of fistulas into the colon or duodenum are also fairly common developments Hemorrhage may occur from an ulcerating malignant lesion Rixford[18] described a case in which distention of the gallbladder with blood resulted in rupture Most neoplasms of the gallbladder are highly malignant[2,19] and appear to grow rapidly They may extend by continuity into the liver, and infrequently they have been known to project themselves into the lumen of the bile ducts or even into the duodenum Metastasis to the liver is found in about 50 per cent of cases at the time of operation and secondary deposits of tumor may also be found in nodes along the cystic duct, in the peritoneum, lungs and mediastinum Deposits of metastatic carcinoma may occur in the pelvic lymph nodes and in rare instances metastasis may occur to the cervical lymph nodes by way of the mediastinal lymphatics, under these conditions Virchow s node may be palpable

Secondary carcinomas of the gallbladder occur chiefly when direct extension occurs from tumors of the stomach, pancreas and colon. These secondary growths are confined largely to the serous coat of the gallbladder, rarely invade the mucous coat and seldom obstruct the cystic duct. Siegert[11] found that secondary neoplasms were less common in females than in males and that they were only infrequently associated with stones.

Symptoms of Carcinoma of Gallbladder.—The symptoms are variable and usually can be accounted for by the preexisting cholelithiasis, the local effects of the tumor itself and the more remote effects of extension and metastasis. The frankly malignant phase of the condition is well described by Musser,[67] who commented on the presence of pain, jaundice, cachexia and a palpable cholecystic tumor; in his series pain was present in about 62 per cent of cases, jaundice in 69 per cent and tumor in 68 per cent. In a majority the tumor was described as hard, painful and tender.

In analyzing the symptoms in a recent series Judd and Baumgartner[90] noted three general groups of cases. In the first, comprising 70 per cent of patients, there was a long antecedent history of biliary colic and flatulent dyspepsia with an abrupt change of symptoms to those of the malignant phase in the later stages of the disease. In a second group, including 22 per cent of their series, the patient's complaints were essentially those of chronic cholecystic disease, with only moderate digestive disturbances and little evidence of cachexia. Obviously this group represents most of the instances in which cancer was discovered accidentally at operation. In a third group of cases, 8 per cent, the clinical syndrome was that of general carcinomatosis with hepatic involvement, ascites and jaundice. In this whole series of 56 cases jaundice was noted in 13 and a palpable tumor in the region of the gallbladder in 29. Hepatic metastasis was found in about one third of the cases at operation or at necropsy.

Any discussion of the mechanism by which symptoms are produced is largely superfluous. In the earlier stages pain is produced by gallstones and associated lesions of the gallbladder and at a later stage by cancerous involvement of the peritoneum and adjacent tissues. Jaundice is referable to compression or invasion of the common duct, to involvement of nodes in the portal fissure or to hepatic metastasis. Intermittent vomiting is common and signs of more or less complete pyloric obstruction may be noted occasionally. In rare cases the duodenum is obstructed by direct pressure or metastatic lesions; the colon may be involved in a similar fashion and signs of intestinal obstruction may occur. The terminal symptoms of cachexia, ascites and hemorrhage are chiefly related to hepatic involvement and to the effects of jaundice; extensive peritoneal carcinomatosis may of itself produce ascites.

Diagnosis, Prognosis and Treatment of Carcinoma of Gallbladder.—The

diagnosis is seldom made by clinical means although frequently it may be suspected In Fawcett and Ripmann's [0] series of 48 cases a positive clinical diagnosis was not made in any instance, and Eusterman[71] reported a somewhat similar experience in a smaller series With a history of previous cholecystic disease the demonstration of a hard, painful and irregularly rounded tumor in the right upper quadrant may lead to a correct diagnosis, hepatic enlargement, jaundice and cachexia seen in conjunction with these findings signify that metastasis has occurred The general failure to diagnose the disease before operation is not remarkable, when one considers that the pain is as a rule neither constant nor characteristic, that jaundice is present in less than half of the cases, and that a palpable tumor is present only slightly more frequently Cholecystography has not been of value except in rare cases, and there are no other pathognomonic laboratory findings Curiously enough anemia is infrequent

The most common error in diagnosis is to regard the symptoms and signs as due to cholelithiasis a mistake which is quite justifiable when one considers that in a majority of cases the cancerous gallbladder contains stones A distended stone filled and calcified gallbladder has been known to simulate carcinoma very closely Because of the jaundice, cachexia and palpable tumor common to both diseases a diagnosis of carcinoma of the head of the pancreas is the next most common error The character of the tumor may be a distinguishing point The globular smooth gallbladder of distention should not be confused with the hard irregular mass noted in primary carcinoma Hepatic syphilis is often characterized by a hard irregular liver, by pain, jaundice, fever and cachexia it should be differentiated by serologic methods in a high percentage of cases Because of the very large diagnostic error, which seems to be unavoidable in primary carcinoma of the gallbladder surgical exploration often is justifiable If the history suggests previous cholecystic disease of the benign type and if there is no conclusive evidence that the malignant phase has been reached surgical measures are clearly indicated It is possible that cholecystographic means of diagnosis of early lesions will be developed eventually but at present the occasional early and therefore operable carcinoma of the gallbladder is almost invariably a chance finding Even if surgical removal is possible the prognosis is almost uniformly bad most of the patients dying within a year Only four patients in Judd and Baumgartner's[200] series lived more than five years after cholecystectomy In Quenu's[™] series, there were 18 operative deaths and of 52 patients who could be traced only 14 were alive a year later and of these only 6 were in good condition The operative mortality is high at least 10 per cent, chiefly because of hemorrhage Many surgeons now avoid interference if a palpable tumor is present, since as Blalock[23] noted operation usually seems to hasten the fatal outcome Even in

cases in which the primary growth was very small metastasis occurred soon after operation Good results are obtained occasionally Magoun and Renshaw[24] reported cases in which patients lived eight, nine and eleven years respectively, after cholecystectomy If any lesson can be learned from a study of cases of primary carcinoma of the gallbladder, it is that early removal of calculous gallbladders will reduce the incidence of malignant disease of the organ

II DISEASES OF THE BILE DUCTS

ANATOMIC ABNORMALITIES

Anomalies of the extrahepatic biliary passages are numerous and are of considerable surgical importance Probably in at least 10 per cent of specimens at necropsy some abnormality of the gallbladder bile duct or adjacent blood vessels can be demonstrated Abnormalities of the gallbladder have been considered in an earlier part of this chapter

The cystic duct may be absent occasionally this is the result of congenital stricture and in such cases the gallbladder is converted into a sort of mucous cyst Reduplication of the cystic duct has also been noted and it may occur in connection with the rare anomaly of reduplicated gallbladder The abnormalities most frequently encountered in respect to the cystic duct pertain to its point of entry into the common duct rarely it may enter into either hepatic duct, and in about 17 per cent of cases the usual angular junction of the cystic and common duct is lacking[33, 25] the cystic duct proceeding parallel with the common duct for variable distances and entering it at various levels and angles It may even enter the duodenum as a separate channel or it may form a long anterior or posterior spiral about the common duct before joining it

The common hepatic duct may be absent both hepatic ducts entering directly into the common duct at its point of union with the cystic duct Accessory hepatic ducts are observed occasionally Flint[34] noted them in about 15 per cent of 200 dissections Rarely the right hepatic duct may enter directly into the gallbladder, a condition which when present would lead to either external biliary drainage or a collection of bile about the liver after the performance of cholecystectomy The common duct may have an abnormal site of entrance into the duodenum and may open separately from the pancreatic ducts Reduplication of the common duct has also been described and in one remarkable case[26] one of the ducts was the site of a choledochus cyst

Important anomalies in the course and distribution of arteries in the region of the gallbladder also are encountered frequently Flint[34] noted 25 cases in his series in which the location of the cystic or gastroduodenal arteries was such

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lymphatic channels of the liver and finally for the maintenance of chronic foci in the walls of the ducts and parietal sacculi

It seems probable that many clinically recognizable instances of biliary infection are dependent on the lighting up of a chronic infectious process in the ducts by episodes of biliary obstruction The most commonly observed type of chronic infection that which accompanies or precedes calculous or noncalculous cholecystic disease is probably an extremely low grade affair which represents repeated mild insults to the finer biliary passages and hepatic parenchyma by toxic substances arising in the portal system or ascending bacterial invasion by organisms of a low degree of virulence Grossly the liver shows capsular scarring in the region of the gallbladder its edge is rounded and edematous and the hepatic parenchyma in the vicinity may be friable or unusually firm Histologic studies show that the process while most conspicuous in the region of the bed of the gallbladder is a diffuse one involving the whole liver it consists mainly of periductal and periportal fibrosis with local collections of lymphocytes and proliferation of the terminal bile ducts Essentially the process appears to represent a periductal lymphangitis it often bears little relation to the degree of cholecystic infection present or to the presence or absence of stones Tissue cultures [8] from the liver in this condition reveal organisms in a small percentage of cases a point of doubtful import in view of the bacterial flora of the presumably normal liver The principal clinical significance of this infectious process lies in the fact that it may apparently progress over a long period until well marked chronic cholangeitis and pericholangeitis develop rarely this process ends with a chronic obliterative lesion of the larger bile ducts[9] Obstruction from any cause may also give an impetus to the sclerosing process and accelerate the spread of infection

The effects of complete obstruction of uninfected bile ducts are best observed in cases of obstruction of the common duct resulting from the growth of an intrinsic or extrinsic carcinoma As the corrosion specimens prepared by Counseller and McIndoe[30] show the result is extreme distention of all the biliary passages involving even the finer biliary radicles the condition is often associated with cystic dilatation or rupture of these structures Associated also with these injuries to the ducts is atrophy of the parenchyma of the liver which is dependent in part on increasing intraductal pressure and in part on obstruction to portal blood flow The condition has been called hydrohepatosis because of its resemblance to hydronephrosis[31] Biliary fibrosis is a late event but it may occur if the affected individual survives for a sufficient period the toxic effects of obstructive jaundice Lieber and Stewart[32] found a rapid progressive proliferation of interlobar and perilobar connective tissue after the second month of obstruction Infection of retained bile with purulent cholangeitis is as a rule a terminal process

as to render them liable to injury during the operation of cholecystectomy Accessory cystic arteries are common, and other anomalous vessels not mentioned in most texts on anatomy may run a tortuous course along the anterior surface of the cystic duct The anomalies of the ducts and adjacent vessels have been reviewed in detail in articles by Eisendrath and Flint Mentzer[227] also has discussed the subject from the standpoint of comparative anatomy and has pointed out that most of the abnormal arrangements which have been found in man represent the normal course of the extrahepatic bile passages in certain animals birds and reptiles The obvious importance of these anomalies lies in the fact that they may greatly increase the technical difficulties of surgical procedures on the bile passages and may lead to accidental injury of these structures notably the common duct, during operation

Cholangeitis, Infection of the Biliary Tract

Most diseases involving the excretory channels of the body are associated with phenomena referable to obstruction infection, or a combination of the two with resultant degenerative changes and infection in the glandular organ drained by these channels All of the diseases of the bile ducts are likewise characterized to a greater or lesser extent by signs of occlusion, of ascending infection and by changes in the parenchyma of the liver For this reason it seems necessary to describe singly and in combination, the general effects of infection and of obstruction on the system of ducts before proceeding with a clinical discussion of diseases of the biliary passages

The intrahepatic biliary passages which extend from the points of entrance of the intracellular canaliculi into the bile capillaries to their final juncture where they fuse to form the right and left hepatic ducts, lie throughout their course in the portal spaces in intimate relation with the portal vein, the hepatic artery the lymphatic vessels and the connective tissue framework of the liver Along the course of the larger intrahepatic ducts are found the parietal sacculi, vestigial structures in the form of blind crypts which open into the lumen of the duct In disease these sacculi serve to harbor infecting microorganisms which may persist even after presumably adequate drainage of the system of ducts has been secured Thus an infectious process that invades the system of ducts will not only expose all of the structures in the portal space to injury, but by extension into the intracellular canaliculi will bring toxic substances directly into contact with the hepatic cells The possibility that such an infection will be disseminated is increased by the presence of lymphatic structures surrounding the wall of the ducts Infection involving the lumens or walls of ducts is thus provided with an ample opportunity for extension to the hepatic cellular structure for widespread dissemination through the periductal

While the pathology of cholangeitis has been thoroughly studied the clinical aspects of the various types and stages of infection of the biliary passages are by no means clearly defined Purulent cholangeitis constitutes an exception, but none of the minor grades of infection of the biliary passages whether acute or chronic, are associated with a definite clinical picture or at least with one that is generally recognized The later stages of the more chronic types of cholangeitis are largely masked by the signs of biliary obstruction and of biliary cirrhosis which are associated with it

Catarrhal Choledochitis

In years past it has been held that one of the causes of so-called epidemic or infectious jaundice was catarrhal inflammation of the common duct with obstruction to its lumen by mucus and epithelial debris The principal argument for the presence of such obstruction has been based on the finding of mucous plugs and similar material in the duodenal contents From the point of view of the pathologist no such condition is known to exist, and most authorities agree that epidemic jaundice is primarily a matter of hepatic cellular injury Studies on hepatic function (hippuric acid synthesis galactose tolerance) seem to bear out this contention There are however some cases of supposed epidemic jaundice which go on to a stage of chronicity with hepatic enlargement, splenomegaly and even ascites[234 235] In such severe cases recovery may and frequently does occur but in exceptional instances the end result is a chronic diffuse hepatitis which is indistinguishable from hypertrophic biliary cirrhosis In such cases chronic cholangeitis may play a part but it seems probable that whatever infection may be present in and about the bile ducts is not necessarily the original cause of the disease Treatment is best directed primarily toward the protection of the hepatic parenchyma For a fuller description of the various types of acute and chronic hepatitis the reader is referred to the chapter on diseases of the liver (see Vol III Chapt VI)

Chronic Infective Cholangeitis

Chronic calculous cholangeitis is mentioned further under the heading choledocholithiasis The chronic cholangeitis with hepatitis which may accompany or precede cholecystic disease of the noncalculous variety may or may not be a cause of clinical symptoms the difficulty being that one cannot often distinguish between the disturbances produced by biliary infection per se and the disease process in the gallbladder Usually there is little fever and scant evidence of an active infectious process That chronic cholangeitis of this type may be responsible for pain in the region of the liver for biliary colic for

The combination of obstruction and infection of the biliary passages produces the maximal amount of injury to the ducts and hepatic parenchyma, this varies with the degree and duration of obstruction and with the extent of preexisting infection, obstruction serving as a stimulus to the spread of the chronic cholangeitis which in many instances is already present In cases of intermittent obstruction produced by stones in the common bile duct, dilatation of the intrahepatic biliary tree, while of considerable extent is limited by the presence of fibrosis in the wall of the ducts as a result of previous inflammation Although in these cases the common duct itself usually is dilated and infected, the most striking change observed consists of active proliferation of connective tissue in and about the smaller bile ducts, the result of biliary retention in previously infected channels Judd and McIndoe[23] concluded from their studies that stones in the common bile duct would produce little serious damage to the hepatic parenchyma if it were not for the chronic infection of the ducts which usually is present before obstruction occurs

In acquired stricture of the ducts which may follow surgical procedures on an infected biliary tree, the progress of the preexisting cholangeitis is more rapid than in obstruction resulting from stone, and the tendency for the hepatic parenchyma to be injured with resultant biliary cirrhosis, is much more pronounced Again, fibrosis limits dilatation of the ducts, and the extra hepatic biliary passages may become involved in an obliterative process With either stone or stricture however, the combination of a progressively spreading infectious process involving the finer bile ducts and adjacent lymphatic structures leads to the destruction of hepatic cells to connective tissue proliferation in the portal spaces and finally to the ultimate formation of biliary cirrhosis At any stage in the course of chronic cholangeitis, whether associated with a stricture or stones an acute ascending infection of the biliary passages may supervene and this may progress to suppuration and the formation of abscess In some pathologic specimens it is possible to distinguish the effects of successive waves of superimposed acute infections which have been followed by healing, either partial or complete

Clinical Syndromes Associated with Infection of the Biliary Passages

Cholangeitis may be defined as an inflammatory process occurring in and around the walls of the intrahepatic biliary passages the pathologic lesions varying from simple catarrhal involvement of the lining epithelium to periductal fibrosis and thickening of the wall of the duct, lymphocytic and leukocytic collections in the connective tissue surrounding the portal spaces and under certain conditions the formation of abscesses in and about the biliary passages

with jaundice The relation of chronic cholangeitis and pericholangeitis to Hanot s cirrhosis is unknown but certainly the two diseases have some factor in common In general it may be said of the chronic infectious processes of the bile ducts that they cannot often be clinically differentiated from the diseases of the gallbladder which accompany them, and that in particular the hepatic lesions resulting from chronic biliary infection are virtually an integral part of the syndrome that we term 'cholangeitis'

Suppurative Cholangeitis

It has already been stated that active suppuration in the biliary passages most frequently represents a lighting up of previous infection in the finer biliary radicles and parietal sacculi and that it may develop in the course of any of the chronic types of cholangeitis or as a late event in hydrohepatosis from malignant stricture of the bile passages Primary ascending biliary infection in the non obstructed system of ducts is not a common occurrence except when there are abnormal connections between the gallbladder and gastrointestinal tract Because of the previously mentioned anatomical peculiarities of the ducts suppuration in these passages represents an extremely serious and often fatal condition The usual precipitating causes are (1) biliary obstruction by stone stricture chronic or subacute pancreatitis or pancreatic neoplasm the first two named furnishing most of the examples of the condition seen in practice (2) parasitic invasion of the biliary passages (3) ascending infections from the gastrointestinal tract which occur particularly following cholecystgastrostomy or cholecystduodenostomy or in the presence of a cholecystduodenal fistula Curiously enough generalized secondary infection of the biliary passages rarely occurs from systemic infection from metastatic hepatic abscesses or from pyogenic granulomas involving the substance of the liver

The *pathologic changes* observed in cases of *purulent cholangeitis* obviously depend on the previous state of infection and dilatation of the biliary passages and on the virulence of the infecting organism The usual invaders are bacilli of the colon group the pyogenic cocci and bacillus aerogenes capsulatus In bile passages which are already sclerosed and dilated bacterial invasion may *be fairly well tolerated and the process may go on to a state of chronic suppuration* such a condition is not uncommon in the presence of a stricture or a stone Grossly the liver is seen to be enlarged and it may be softer than normal. Dilatation of the biliary passages is the rule the intrahepatic ducts exude pus on section and the bile may be foul turbid and contain calculous mud Miliary abscesses about the finer bile passages often are a striking feature and the low power lens will reveal large numbers of these lesions Larger

vague reflex digestive disturbances and for transient jaundice seems fairly well established In certain cases of this type, in which the abdomen has been explored the disease in the gallbladder has been slight and that in the bile ducts and liver the principal finding The hepatic changes noted in such instances have been variable in extent the common duct has been described as chronically inflamed or dilated enlarged lymph nodes in the vicinity indicating the infectious nature of the condition Under such circumstances cholecystectomy may relieve the symptoms but it does not do so in every case In some cases another operation at a later date has revealed little or no change in the state of the liver and biliary passages in other cases there has been progression of the hepatic damage To attribute persistent biliary colic and related symptoms to the residuum of cholangeitis and hepatitis in such cases seems a somewhat questionable practice but often no better explanation is available Prolonged surgical drainage of the common duct by a T tube may permanently relieve such patients thus strengthening the argument that chronic biliary infection may be responsible for the symptoms

There is one type of choledochitis and associated cholangeitis, which is not infrequently encountered clinically and which deserves special mention Usually described as noncalcareous inflammatory biliary obstruction associated with cholecystitis it is seen most frequently in association with subacute pancreatitis Walters[36] who has described the surgical findings in some detail, was of the opinion that the inflammatory process arises in the gallbladder, extends by continuity to the wall of the common duct and eventually involves the pancreas the gallbladder usually is the site of an acute or subacute cholecystitis but it contains no stones the common duct is dilated inflamed and its walls unaltered the bile is turbid and from it the colon bacillus has been isolated The head of the pancreas is enlarged and indurated the liver does not appear to be grossly damaged The symptoms of the condition are essentially those of choledocholithiasis among them biliary colic jaundice and fever being conspicuous Cholecystectomy and prolonged surgical drainage of the common duct usually is curative the choledochitis and pancreatitis subsiding promptly once the original focus of infection is removed

The *symptoms of the less active types of chronic noncalculous cholangeitis and hepatitis* are practically indistinguishable from those of chronic cholecystic disease although the presence of chronic or intermittent jaundice and slight fever will, occasionally suggest the presence of biliary infection It is unusual for a non suppurative cholangeitis of this type to progress to a stage where injury to the bile ducts is serious but in rare cases chronic obliterative cholangeitis with persistent jaundice may develop on such a basis and actual cirrhosis occasionally may ensue I have seen one case in which ascites developed twelve years after surgical exploration for chronic cholecystitis and hepatitis

relative rarity of cholangeitis under these conditions Rarely an ascending infection of the bile passages is said to develop on the basis of duodenitis or of an infected duodenal diverticulum in a few cases a similar type of infection has been noted after partial gastrectomy The absence of hydrochloric acid with subsequent changes in the duodenal bacterial flora probably explains such an occurrence.

Harnisch[39] and others have called attention to a form of cholangeitis usually secondary to biliary obstruction by stone or carcinoma that is characterized by a markedly septic febrile reaction by jaundice and by moderate enlargement of the liver Anemia and leukocytosis were features in one of Harnisch s cases and streptococci were isolated from blood cultures.

Because the chronic septic course is the most characteristic feature of this syndrome the condition has been called cholangeitis lenta. Cases of this type have been described which resembled biliary cirrhosis with associated splenomegaly but in a majority of the cases on record the most striking clinical features were the febrile state and the relatively inconspicuous nature of the few symptoms to suggest the presence of a primary hepatic lesion

Treatment of Suppurative Cholangeitis — Treatment of suppurative cholangeitis in general is best directed toward the underlying causes of the condition Prophylaxis is important infected and stone filled gallbladders should be removed and obstructing lesions of the biliary passages should be corrected as soon as a diagnosis can be made before the sequelæ of obstruction and infection damage the ducts and liver beyond repair

Early in the course of a purulent cholangeitis before the finer biliary passages and hepatic parenchyma are involved surgical drainage of the common duct may be curative When suppuration is extensive and multiple miliary abscesses form in the hepatic parenchyma surgical treatment may be of little avail In such instances supportive measures may tide the patient over until localization occurs and abscesses of larger size which may be surgically drained form Under such conditions the prognosis usually is poor but in an occasional case the process will become chronic and the patient will survive for a time This is particularly true of patients with acquired stricture of the ducts who may weather numerous exacerbations of cholangeitis even after abscesses have drained spontaneously [40] Biliary cirrhosis and infection ultimately will result in a fatal outcome in these cases unless the normal flow of bile into the intestinal tract can be reestablished There is no specific medical treatment of value the intravenous injection of such dyes as mercurochrome does not seem to affect the condition in any way and there is little evidence to indicate that any medication administered orally is able to disinfect the bile passages

solitary abscesses may be a feature in the more chronic cases, these abscesses may rupture into the subdiaphragmatic space, penetrate into the pleura and even discharge through bronchobiliary fistulas The suppurative process may involve the pancreas or peritoneum or it may extend to the portal vein with resulting pylephlebitis

The *symptoms of suppurative cholangeitis* are often overshadowed by the picture of biliary obstruction Chills fever a temperature indicating a septic condition and toxemia are common and often pursue an intermittent course with remissions and relapses As the condition progresses, deepening jaundice, wasting and cachexia develop The liver ordinarily is enlarged and diffusely tender on pressure but in cases of stricture or stone signs of localized infection may not be conspicuous even with extensive suppuration The right leaf of the diaphragm may be partially fixed and elevated and signs of pleural involvement are not infrequent especially if an abscess points toward the dome of the liver Marked leukocytosis and a great increase in the sedimentation time are among the more striking laboratory findings positive blood cultures sometimes may be obtained The level of serum bilirubin varies with the degree of biliary obstruction and the amount of hepatic cellular damage

Diagnosis of Suppurative Cholangeitis — Diagnosis of suppurative cholangeitis is made more often by inference than by the demonstration of characteristic symptoms or signs and in numerous instances the presence of biliary suppuration may not be detected except at operation or necropsy The development of severe constitutional symptoms in the course of cholelithiasis or in the presence of biliary obstruction from neoplasm suggests the diagnosis, repeated bouts of fever and deepening jaundice in the presence of stricture likewise are almost pathognomonic In cases in which patients have not previously been subjected to surgical procedures malaria and amebic abscess of the liver must be excluded Pylephlebitis which may accompany suppuration in the biliary passages can hardly be differentiated with certainty, a progressive enlargement of the spleen favors the diagnosis of involvement of the portal vein Hepatitis and cirrhosis rarely produce such severe systemic reactions but it must be recalled that in these diseases cholangeitis may develop as a late complication

In ascending infections secondary to cholecystenterostomy the clinical manifestations are less severe than if biliary obstruction is present and intermittent fever a tender liver and variable slight jaundice may be the principal signs While suppurative cholangeitis is an invariable development in experimental cholecystgastrostomy[37] it is not a common sequel in clinical cases at least in those in which the operation is performed for the relief of obstructive jaundice Wangensteen[38] recently has cited a case and commented upon the

reported in which one of a pair of binovular twins has suffered from congenital obliteration of the biliary passages the other twin being normal [19-20] Such cases can hardly be explained on the basis of any prenatal hepatotoxic process The most likely cause for the condition appears to be congenital malformation of the bile ducts the biliary cirrhosis being a purely secondary affair Ylppo[21] in reviewing the subject called attention to the work of the earlier embryologists, who believed that the bile ducts in the fetus were originally patent later becoming solid by a process of epithelial proliferation and still later becoming permanently canalized It is believed that this process of secondary canalization involves first the common duct and then the hepatic duct cystic duct and gallbladder in that order If this explanation is correct the process of congenital stricture of the ducts may easily be accounted for The numerous congenital anomalies which have been associated with the condition seem to be in accord with the theory of congenital malformation Sweet has reported three cases in one family, in two of which the condition was associated with congenital cardiac anomalies and he collected six similar examples of such familiar incidence from the literature Coburg[23] has called attention to the frequency with which cystic kidneys polydactylism hemangiomas and other congenital abnormalities were associated with atresia of the ducts Helwig[24] has cited two cases in which there were multiple spleens Holmes[25] felt that congenital obliteration of the lumen is the primary factor in most cases and that in others narrowing of the lumen exists at birth subsequent infectious processes completing the process of occlusion This view would account for the rare cases in which jaundice develops late after birth

Pathology of Congenital Obliteration of Bile Ducts

The ducts in the involved region are reduced to fibrous cords or they may be absent altogether Dilatations of the ducts above the point of obstruction is the rule The liver is large greenish and usually shows gross and microscopic evidence of biliary stasis and fibrosis icteric pigmentation of the cells biliary thrombi and proliferation of the intrahepatic bile ducts are common findings Splenomegaly is not uncommon particularly when the atresia involves the lower end of the common duct In this location the obliterative process may also occlude Wirsung s duct and thus cause associated changes in the pancreas a point of considerable importance in the consideration of treatment.

Symptoms of Congenital Obliteration of Bile Ducts

Males appear to be more commonly affected than females The principal

Congenital Obliteration of the Bile Ducts

Congenital obliteration of some portion of the extrahepatic biliary passages is not a particularly uncommon condition. Holmes[41] collected 100 cases in 1916 and numerous individual reports have appeared since then. The essential abnormality consists in fibrous obliteration of some part of the extrahepatic biliary apparatus; if the common or hepatic ducts are involved obstructive jaundice results with hepatic parenchymal damage ranging from areas of simple atrophy to actual cirrhosis. The extent of the damage done to the liver appears to depend on the duration of life of the affected individual. The site of obliteration is extremely variable; impervious cystic ducts seem to be fairly common. Next in frequency is obliteration of the common duct and third involvement of the hepatic ducts; multiple areas of occlusion are not uncommon and Holmes[42] noted that in half of the cases in which the common duct was involved the cystic and hepatic ducts were involved also. The intrahepatic portions of the system of ducts are only rarely involved; there are two recent reports of fibrous obliteration or absence of these channels.[43, 44]

Etiology of Congenital Obliteration of Bile Ducts

Numerous theories have been advanced to explain the etiology of congenital obliteration of the bile ducts, such as that the condition may result from, (1) lesions produced by congenital syphilis, (2) those referable to fetal peritonitis, (3) a catarrhal condition within the ducts themselves superimposed on biliary cirrhosis originating in intrauterine life, and (4) failure of normal development of the lumen of the duct as a result of congenital malformation. The first two theories may be dismissed largely because of lack of evidence. In most cases reported recently the Wassermann reaction has been negative, and there has been no evidence of congenital syphilis in other organs. In rare instances, however, syphilis plays a definite role, as in a case recently reported by Smith and Ball.[45] Fetal peritonitis is rarely if ever a factor, as studies at necropsy show. The third theory, that of obliterative cholangeitis affecting the ducts of a liver previously involved by cirrhosis, has been championed by Rolleston,[1, 3] his arguments being based chiefly on the rather extensive cirrhotic lesions noted in many cases. These changes in the liver have been attributed to some toxin arising in the maternal circulation. However, biliary cirrhosis of this degree can be produced experimentally by ligation of the common duct[46] and it is also true that the processes of fibrosis appear to progress more rapidly in young animals. Likewise it is apparent that cirrhosis is not an infrequent finding in biliary stasis from whatever cause.[47-48] The theory of primary cirrhosis in uterine life thus is difficult to sustain. Cases have been

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Prognosis and Treatment of Congenital Obliteration of Bile Ducts

Until sufficient time has elapsed to establish a positive diagnosis the prognosis must be guarded Without surgical intervention the outlook is bad few patients surviving for more than six months In the exceptional cases in which patients lived longer biliary obstruction probably was incomplete Surgical relief of the obstruction is the only procedure that offers the slightest possibility of benefit and this can of course be accomplished only with considerable risk If the patient is in reasonably good condition and if there is no evidence of impending hepatic insufficiency or active bleeding operation certainly should be advised Holmes[41] noted that 16 per cent of the cases in his series should have been amenable to some type of surgical treatment such as cholecystenterostomy and Ladd[248] found that in eight of eleven cases the obstruction was at least theoretically amenable to operative relief When because of obliteration of the hepatic or cystic ducts it is not possible to divert the bile into the intestine by anastomosing the gallbladder an external fistula may be formed with the hope that it may subsequently be transplanted Hess[257] recommended that the pancreatic ferments be studied by means of intubation with a duodenal catheter before surgery is considered. If neither lipase nor trypsin can be demonstrated it may be assumed that the pancreatic ducts are involved and that the situation therefore is virtually hopeless

Congenital Cystic Dilatation of the Extrahepatic Bile Ducts

The so-called choledochus cysts are in reality the result of extreme dilatation of the common duct The condition is primarily congenital and may be likened to congenital hydronephrosis idiopathic dilatation of the esophagus or Hirschsprung s disease Disturbance in innervation of the system of ducts with failure of normal relaxation of the sphincter of Oddi has been considered as a possible causative factor Among other theories mentioned by various writers as to its etiology are (1) congenital malformation[250] (2) abnormal or angular insertion of common duct into the duodenum with kinking and obstruction of the ducts[251] (3) a valve like arrangement of the intraduodenal segment of the common duct or congenital narrowing of this portion[26] (4) congenital weakness of the wall of the duct (5) trauma including increased intra abdominal pressure from an enlarged uterus and (6) aberrant pancreatic adenomas causing obstruction or injury to the wall of the duct[250] A completely satisfactory explanation for all of the reported cases is not at present available but some interference with normal drainage of the common duct which may be due either to anatomic lesions or to changes in sphincteric tone may be inferred such a condition coupled with a congenitally

presenting symptom is jaundice which develops from a few days to a few weeks after birth and increases until the skin assumes a deep greenish hue The urine is bile stained and determinations of serum bilirubin show elevation above the normal values The stools are acholic even the meconium stools do not appear to contain bile pigments The liver may be enlarged at birth or become so shortly afterward Splenomegaly, which is a common finding, develops somewhat later, and both the liver and spleen may continue to enlarge during the life of the patient Nutrition usually is well maintained for a time and then falls off with the onset of vomiting and digestive disturbances Subcutaneous hemorrhages or bleeding from the umbilicus and gastrointestinal tract are late developments and may precede the onset of hepatic insufficiency In exceptional cases[10, 20] ascites developed before death Convulsions may occur late in the course of the disease, sometimes because of intracranial bleeding

Numerous studies on the metabolism of fat and nitrogen have been made in these cases the results being somewhat variable and dependent on the general nutrition of the subject and the patency of the pancreatic ducts In general, it has been found that fat is well split but poorly absorbed and that nitrogen absorption is within normal limits[14, 16, 7] A negative calcium balance has been noted, but the absorption of phosphorous appears normal in the few cases in which it has been studied

Diagnosis of Congenital Obliteration of Bile Ducts

Theoretically diagnosis should be simple enough, since there is hardly any other cause for permanent and complete obstructive jaundice in the newborn Icterus neonatorum is most likely to cause confusion, but the persistently acholic stools and deepening jaundice of patients with congenital atresia should differentiate the two conditions Umbilical infection may cause sepsis and jaundice, and it must be excluded

The familial type of hemolytic icterus may under exceptional circumstances also require differentiation Intrahepatic types of jaundice are rare in the new born do not permanently occlude the bile ducts and as a rule, should clear up spontaneously within a reasonable time

Syphilis may be excluded by the finding of a negative Wasserman reaction but in doubtful cases particularly if syphilis can be demonstrated in either parent a therapeutic test may become necessary As Holmes[12] has pointed out it may be very difficult to establish a diagnosis of congenital obliteration of the bile ducts during the early weeks of life but with the passage of time the persistence of complete biliary obstruction identifies the condition

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Congenital Cystic Dilatation of the Extrahepatic Bile Ducts

The so-called choledochus cysts are in reality the result of extreme dilatation of the common duct The condition is primarily congenital and may be likened to congenital hydronephrosis idiopathic dilatation of the esophagus or Hirschsprung's disease Disturbance in innervation of the system of ducts with failure of normal relaxation of the sphincter of Oddi has been considered as a possible causative factor Among other theories mentioned by various writers as to its etiology are (1) congenital malformation[60] (2) abnormal or angular insertion of common duct into the duodenum with kinking and obstruction of the ducts[261] (3) a valve like arrangement of the intraduodenal segment of the common duct or congenital narrowing of this portion[7] (4) congenital weakness of the wall of the duct (5) trauma including increased intra abdominal pressure from an enlarged uterus and (6) aberrant pancreatic adenomas causing obstruction or injury to the wall of the duct[262] A completely satisfactory explanation for all of the reported cases is not at present available but some interference with normal drainage of the common duct which may be due either to anatomic lesions or to changes in sphincteric tone may be inferred such a condition coupled with a congenitally

presenting symptom is jaundice, which develops from a few days to a few weeks after birth and increases until the skin assumes a deep greenish hue The urine is bile stained and determinations of serum bilirubin show elevation above the normal values The stools are acholic, even the meconium stools do not appear to contain bile pigments The liver may be enlarged at birth or become so shortly afterward Splenomegaly which is a common finding, develops somewhat later and both the liver and spleen may continue to enlarge during the life of the patient Nutrition usually is well maintained for a time and then falls off with the onset of vomiting and digestive disturbances Subcutaneous hemorrhages or bleeding from the umbilicus and gastrointestinal tract are late developments and may precede the onset of hepatic insufficiency In exceptional cases[0, illegible] ascites developed before death Convulsions may occur late in the course of the disease sometimes because of intracranial bleeding

Numerous studies on the metabolism of fat and nitrogen have been made in these cases the results being somewhat variable and dependent on the general nutrition of the subject and the patency of the pancreatic ducts In general, it has been found that fat is well split but poorly absorbed and that nitrogen absorption is within normal limits[14, 26, 7] A negative calcium balance has been noted but the absorption of phosphorous appears normal in the few cases in which it has been studied

Diagnosis of Congenital Obliteration of Bile Ducts

Theoretically diagnosis should be simple enough, since there is hardly any other cause for permanent and complete obstructive jaundice in the newborn Icterus neonatorum is most likely to cause confusion, but the persistently acholic stools and deepening jaundice of patients with congenital atresia should differentiate the two conditions Umbilical infection may cause sepsis and jaundice and it must be excluded

The familial type of hemolytic icterus may, under exceptional circumstances also require differentiation Intrahepatic types of jaundice are rare in the new born do not permanently occlude the bile ducts and as a rule should clear up spontaneously within a reasonable time

Syphilis may be excluded by the finding of a negative Wasserman reaction but in doubtful cases particularly if syphilis can be demonstrated in either parent a therapeutic test may become necessary As Holmes[12] has pointed out it may be very difficult to establish a diagnosis of congenital obliteration of the bile ducts during the early weeks of life but with the passage of time the persistence of complete biliary obstruction identifies the condition

jaundice with biliary colic A tumor arising in the right hypochondrium which may be of large size is the salient point on which diagnosis must rest Rarely two tumors have been noted one the distended common duct the other the distended gallbladder In a few cases increase in the size of the abdominal tumor after a full meal has been described due presumably to a flow of bile during the process of digestion Numerous observers have described a valvular arrangement in the wall of the cyst which allows the cyst to empty itself under such conditions the icterus may diminish or disappear In spite of the size of the tumor and its close relation to the duodenum interference with the emptying of the stomach is only infrequently mentioned Morley[66] however described a case in which the duodenum was obstructed

Diagnosis Prognosis and Treatment of Congenital Dilatation of Bile Ducts

The presence of intermittent jaundice in a young person with a large tumor in the right hypochondrium may conceivably lead to a correct diagnosis but according to Zinninger and Cash[67] only three correct preoperative diagnoses are on record The condition has been mistaken most frequently for an echinococcus cyst a pancreatic cyst or a distended gallbladder The prognosis is poor unless surgical drainage of the dilated duct can be accomplished The mortality is high if external drainage alone is instituted thirty-one of thirty four patients so treated having died Seneque and Tailhefer[69] and Judd and Greene[64] recently have reviewed the surgical results and have concluded that an anastomosis between the dilated duct and the gastrointestinal tract is the treatment of choice McWhorter[65] recommends this procedure together with excision of a portion of the cystic wall to improve biliary drainage In the more recently reported cases the surgical results of choledochoduodenostomy have been quite satisfactory

Acquired Benign Stricture of the Bile Duct

This condition may be defined as an occlusive or obliterative process involving the common and hepatic ducts which in a large majority of cases appears at varying intervals after the performance of cholecystectomy Since cholecystectomy has been performed more and more frequently and by surgeons of various degrees of technical proficiency the number of strictures appears to be increasing Eliot[70] reported a considerable series of cases of stricture in 1918 principally collected by personal correspondence Judd in 1928[71] reported a large series of cases in which he had performed secondary operations for stricture and many reports of smaller series[72] have appeared since that date

weakened wall, could result in dilatation of the degree observed in these cases

Incidence of Congenital Dilatation of Bile Ducts

The condition is rare Judd and Greene[64] found only one case at the Mayo Clinic in 17,381 in which operation was performed on the biliary passages in a twenty year period McWhorter (1924)[65] reported one case and cited forty seven others from the literature, and Gross (1933)[66] collected reports of fifty two cases in which the patients were children Zinninger and Cash (1932)[67] recently have made an extensive review of the literature Finding only eighty two entirely authentic cases, they pointed out that many of the cases reported were probably not true examples of cystic dilatation of the common ducts and that there were certainly marked differences in the pathologic findings reported

Pathology of Congenital Dilatation of Bile Ducts

The similarity of the observations made at operation in these cases has been commented on by recent writers A large cystic tumor, often about 15 cm in diameter and partially retroperitoneal is seen just below the liver pushing the stomach to the left and the duodenum downward the ascending and transverse portions of the colon also are displaced to the left and downward In most instances the gallbladder is described as normal in size or was not visualized occasionally it has been found to be distended In a majority of cases the tumor appears to involve only the extraduodenal portions of the common duct but in at least three recorded instances it extended so low that the pancreatic duct apparently entered the cyst The size of the tumor, the thickness of its wall and the character of its contents have been variable, and examination of the wall of the duct has revealed no definite changes The state of the liver appears to depend on the completeness and duration of the obstruction the lesions in the liver ranging from areas of atrophy or necrosis to chronic cholangeitis or actual cirrhosis

Symptoms of Congenital Dilatation of Bile Ducts

In contradistinction to congenital atresia which is more common among males this condition affects females predominately In most instances symptoms are apparent before the age of ten years but there have been numerous cases described in adults in which long periods of latency were a peculiar feature The clinical picture is that of continuous or intermittent obstructive

and third, it is the least distensible portion of the duct When the surgeon encounters a stricture the ordinary landmarks are obliterated and it is often difficult or impossible to identify the distal portion of the duct or even to determine the exact site of the stricture Frequently a substantial portion of the extrahepatic system of ducts appears to be missing and under such circumstances the surgeon must content himself with isolation of one or the other hepatic ducts

Pathology of Benign Stricture of Bile Duct

The essential pathology of the condition is that of continuous or intermittent biliary obstruction with the added element of an extensive and progressive chronic cholangeitis and pericholangeitis Hydrohepatosis and periportal fibrosis of varying degrees are an essential part of the pathology of stricture and if surgical repair of the affected ducts is not carried out early extreme degrees of biliary cirrhosis ultimately result Even in cases of stricture of short duration splenomegaly is a very common finding Obstruction to the portal circulation with ascites and dilatation of collateral venous channels may be a feature of certain advanced cases in these the gross and microscopic appearance of the liver may be that of portal cirrhosis In other cases infection in the biliary passages dominates the picture suppurative cholangeitis with the formation of multiple abscesses is a frequent development and large abscesses occasionally rupture externally or penetrate the diaphragm forming bronchobiliary fistulas There are few conditions involving the bile ducts in which so wide a variety of hepatic lesions may be encountered, or in which hepatic parenchymal infection and injury play so prominent a part

Symptoms of Benign Stricture of Bile Duct

Three types of symptoms are seen the difference depending chiefly on the rapidity with which the common duct is occluded In the first jaundice develops promptly after operation gradually deepens and later remains more or less constant in the second there is prolonged postoperative biliary drainage with intermittent jaundice increasing as the external flow of bile diminishes the icterus finally becoming relatively constant as the fistula closes In the third and least common type the postoperative convalescence is normal and the patient may be quite comfortable for a period of months or even years then jaundice appears often without accompanying pain or colic Intermittent at first it later becomes constant In all three types attacks of biliary colic less severe on the average than those associated with stone may be noted these attacks are accompanied by fever chills and temporary increases

The mechanism by which such strictures are produced is of great clinical and medicolegal significance It is difficult to be certain that surgical trauma to ducts is the sole etiologic factor since there are a few cases on record in which strictures developed presumably as the result of an inflammatory sclerosing process of the biliary passages of patients who had never been operated on While admittedly rare the existence of a primary obliterative cholangeitis not associated with the formation of calculi or previous surgical procedures is well established in the cases reported there has been diffuse contraction of the common and hepatic ducts extending well into the hilum of the liver with thickening of the wall of the duct and enlargement of periductal lymphatic structures The outer coats of the duct are affected primarily, the lining mucosa being fairly well preserved apparently the initial process is pericholangeitis Trauma to the lining epithelium of the common duct by stones cannot be an important factor In fact there have been only four cases at the Mayo Clinic in which a stone in the common duct appeared to produce local stricture and in all of these cases the narrowing was confined to the pancreatic portion of the duct a few other cases have been noted in which inflammatory processes arising in a gallbladder that was adherent to the common duct or arising in the stump of the cystic duct after cholecystectomy, produced stricture of the common duct by direct extension

In the individual case of acquired stricture the element of surgical trauma is difficult of appraisal In some cases direct injury is done to the common duct because of the difficulties encountered when anomalies of the cystic duct or adjacent blood vessels were present or because of the distortion of parts produced by disease In fact it seems likely that minor degrees of injury affecting the common duct during cholecystectomy must be fairly common, and that they probably pass unrecognized at the time of operation and heal spontaneously Experimental evidence indicates that the common duct can repair its injuries with considerable facility, and it undoubtedly does so more often than is generally believed In the occasional case, however trauma plus latent or active infection in the wall of the duct and adjacent lymphatic structures starts the process of obliterative cholangeitis and from this there eventually results stricture In about half of the cases the process is fairly well localized annular and tubular

The commonest site of stricture is the juncture of the cystic and common ducts, the next most common the supraduodenal portion of the common duct strictures at the papilla or of the hepatic ducts are much less common The usual location at the point of termination of the cystic duct probably is determined by three factors first it is the point most likely to be injured by operations on the gallbladder second the one most likely to be involved by an extension of inflammation from the gallbladder through the cystic duct

and third it is the least distensible portion of the duct When the surgeon encounters a stricture the ordinary landmarks are obliterated and it is often difficult or impossible to identify the distal portion of the duct or even to determine the exact site of the stricture Frequently a substantial portion of the extrahepatic system of ducts appears to be missing and under such circumstances the surgeon must content himself with isolation of one or the other hepatic ducts

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in the depth of the jaundice Pruritus is common and frequently severe, and extreme irritability of the digestive tract also is a common feature

On physical examination the liver is found to be enlarged, very firm and often irregular the spleen is almost always enlarged, especially in the more chronic cases Persistent biliary fistulas are not infrequent, they may develop spontaneously or result from previous attempts at operative repair A factitious dermatitis melanosis of the skin and subcutaneous hemorrhages are common The stools in a majority of cases are not completely acholic, and duodenal intubation reveals small amounts of bile in about three cases out of four

Since biliary obstruction is not often complete moderate degrees of jaundice are the rule The average level of serum bilirubin was 10 mg or less in 75 per cent of Weir s[73] series Moderate anemia often of a macrocytic type is a feature in many cases it may be due primarily to hepatic cirrhosis or secondarily to hemorrhage from various sources Appropriate tests of hepatic function usually will indicate moderate or advanced injury to the hepatic parenchyma, the coagulation time of the blood is considerably prolonged in a majority of cases, and rarely thrombocytopenia will develop with uncontrollable bleeding[240]

In cases of stricture of long standing the clinical picture may gradually approach that of portal cirrhosis emaciation hemorrhages from the skin and mucous membranes and signs of hepatic insufficiency develop and in an exceptional case ascites and edema appear as terminal manifestations I have seen one patient with a stricture of the common duct of eight years duration develop ascites and die in hepatic coma following hemorrhage from esophageal varices

Diagnosis of Benign Stricture of Bile Duct

If biliary obstruction develops shortly after cholecystectomy in a case in which jaundice has not previously been present the diagnosis at once suggests itself This is particularly true if an external biliary fistula is present which discharges intermittently and acts as a sort of regulator for the degree of jaundice Postoperative jaundice and intermittent fever which persist in spite of the presence of a draining fistula are at least as commonly caused by stricture as by any other condition such as stone a residual stone in the common duct a small neoplasm at the papilla overlooked at the original operation and primary biliary cirrhosis are the principal sources of diagnostic error In the occasional case in which the occlusive process develops spontaneously or long after operation accurate diagnosis is difficult or impossible

Prognosis and Treatment of Benign Stricture of Bile Duct

As Mann and his associates [74] have shown, the hepatic parenchyma cannot regenerate itself in the presence of obstructive jaundice Unless the continuity of the biliary passages can be restored and the element of ascending infection controlled, the prognosis is absolutely bad progressive damage to the hepatic parenchyma ultimately leading to a fatal outcome A suppurative cholangeitis an obstructive biliary cirrhosis or both are the usual terminal developments Death in hepatic coma is not infrequent, and a pronounced hemorrhagic tendency figures largely in the mortality

Cases in which numerous attempts have been made to repair the stricture are often seen a fact which impresses one with the tolerance of some patients to the presence of prolonged biliary obstruction Certain individuals with incomplete occlusion of the ducts by stricture have been jaundiced intermittently for years their continued existence being possible because of partial patency of the bile passages and because of the fact that the biliary infection present was of relatively low grade A similar tolerance has been noted in experimental animals and is of course referable to the enormous reserve functions of the liver

Treatment is purely surgical and because of the extreme technical difficulties presented it is largely a matter for experts The general condition of many of these patients is bad they tend to bleed the hepatic reserve is insufficient to stand any strain and the problem of isolating and repairing the strictured ducts is a most difficult one Excision of the stricture and reconstruction of the duct over a catheter is sometimes possible oftener hepaticoduodenostomy or choledochoduodenostomy is the only feasible procedure and occasionally the sole surgical recourse is establishment of an external biliary fistula which can be transplanted into the duodenum at a later date In skilled hands excellent results can be obtained provided damage to the ducts and hepatic parenchyma is not too far advanced In Judd s [1] series about two-thirds of the patients were much improved or were completely cured The damaged state of the hepatic parenchyma the persistent cholangeitis and the tendency for stricture to reform at the site of anastomosis or in the reconstructed ducts all stand in the way of successful treatment. Adequate preoperative treatment with high carbohydrate diets intravenous infusions of glucose and transfusions is essential and may considerably reduce the operative risk

CHOLEDOCHOLITHIASIS

Of the various syndromes produced by diseases of the bile ducts those resulting from the presence of stones are the ones most commonly seen In

few conditions can the cause of the symptoms be at times so obvious and at other times so obscure The clinical criteria of choledocholithiasis are notoriously fallible The symptoms varying with the degree and duration of biliary obstruction, the extent and virulence of associated infection and the amount of damage to the hepatic parenchyma may imitate practically all of the various pathologic conditions in which the ducts and the liver may be involved.

Etiology, Incidence and Distribution of Choledocholithiasis

The majority of stones that reach the common duct almost certainly originate in the gallbladder, probably a few pure pigments or calcium bilirubinate stones form in the ducts themselves especially if there is biliary stasis as a result of the presence of other stones or strictures It seems likely that most stones are quite small when they reach the common duct and that they there increase in size Occasionally very large stones are found which could not have passed through the cystic duct There are rare cases on record in which stones have repeatedly reformed in the common duct in the absence of any visible obstruction to biliary flow or of gross signs of infection some of these stones may have had their origin in the intrahepatic bile passages Pigment stones are known to form repeatedly in the ducts following crises of blood destruction in familial hemolytic jaundice It should be emphasized that the size of the stone or stones has little to do with the character of the symptoms

For information as to incidence and distribution of stones in the common duct one may refer to Judd and Marshall[2, 5] who recently have analyzed 1,768 consecutive cases verified at operation collected during a period when about 13 000 gallbladders containing stones were removed In about 65 per cent. of the cases cited by them both the gallbladder and ducts contained stones They also noted that it was about ten times as common to find stones free in the common or hepatic ducts as it was to encounter them impacted in the ampulla Intrahepatic stones were rare Judd and Burden [6] recorded only two cases, in both of which the condition was found at necropsy As is the case with calculous cholecystic disease females in their series were affected by choledocholithiasis about twice as often as males No age appeared exempt, but the majority of patients were in the fifth and sixth decades of life, and in a substantial number the condition made its first appearance in aged individuals

Pathology of Choledocholithiasis

The pathologic changes secondary to the presence of stones in the common duct are a combination of those produced by biliary obstruction and by in

fection of the biliary passages the extent of such changes depending on the length of time stones have been present in the duct the degree and duration of recent obstruction the amount of damage done to the intrahepatic ducts and to the liver and the virulence of infecting organisms in the biliary passages The common duct usually but not invariably is dilated above the point of obstruction the process of distention extending to the finer biliary passages as corrosion specimens show[30] On opening the common duct one finds either cloudy infected bile mixed with biliary mud or else in obstruction of long standing white bile The gallbladder if present is most often found to be contracted or atrophic, and it either contains stones or shows evidence of previous chronic inflammatory change less commonly associated stones in the cystic duct may produce hydrops or empyema of the gallbladder as a complicating factor Since a stone in the ampulla may obstruct the flow of pancreatic secretion, and since biliary infection may readily extend to the pancreas even in the absence of obstruction of Wirsung s duct chronic fibrous pancreatitis hemorrhagic pancreatitis or cystic enlargement of the pancreatic ducts are noted frequently Rarely pressure of a large stone in the common duct may compress the portal vein thus favoring the development of pyle phlebitis

Grossly the liver is found to be enlarged discolored and its edge rounded its surface may show evidence of chronic hepatitis or of obstructive biliary cirrhosis a deep greenish mottled discoloration is indicative of extensive parenchymal damage and surgeons regard this appearance as indicative of a grave prognosis particularly if the ducts contain white bile On microscopic examination sections of the liver may reveal the widest possible range of lesions including atrophy and bile staining of the cells about the central veins periportal fibrosis or in cases of long standing obstruction obstructive biliary cirrhosis The processes of repair and regeneration may be seen side by side with destructive or inflammatory lesions Chronic cholangeitis with leukocytic infiltration about the finer biliary passages and proliferation of the bile capillaries is common acute inflammatory lesions and localized abscesses of varying size arising in the bile ducts may also be encountered Rarely obstruction by stone appears to lead to a subacute atrophy of the hepatic parenchyma[77]

Symptoms of Choledocholithiasis

It would be desirable if it were possible to set forth here a method of differentiating the symptoms of uncomplicated calculous cholecystic disease, those produced by the stone filled gallbladder with associated stone in the common duct and those produced by a stone in the common duct after cholecystectomy If such a sharp distinction in symptoms were possible, which is

unfortunately not the case, the problems, which daily confront diagnosticians and surgeons would be much simplified One can only enumerate the usual symptoms and call attention to the many instances in which they are atypical or absent

The classical symptoms of stone in the common duct are those of biliary colic with variable jaundice and the intermittent hepatic fever of Charcot There is often an antecedent history of biliary colic without jaundice, indicating the entrance of a stone into the cystic duct, as this structure dilates and allows the stone to enter the common duct jaundice supervenes to be relieved when the stone passes the ampulla or floats back into the dilated common duct The ball valve feature of calculous obstruction explains the usual intermittent character of the pain and the variations in the depth of the jaundice If stones are closely packed in the ampullary portion of the duct, the classic symptoms just mentioned are somewhat more likely to be present, also stones in this situation may produce colics of unusual severity and duration with residual aching pain and tenderness and it is chiefly in this region that stones may be impacted firmly enough to produce almost total obstruction to the flow of bile A stone lying free in the supraduodenal portion of the duct often does not produce marked obstruction and consequently, not so characteristic a clinical picture The presence of the gallbladder obviously will alter the clinical picture no matter where stones may be located in the common duct since if this organ is functioning at all it is capable of acting as a distensible reservoir and thus may delay the onset of jaundice Intrahepatic stones appear to produce no definite or characteristic symptoms unless they be those of chronic jaundice sepsis and suppurative cholangeitis, only a very few such cases have ever been recognized clinically or at operation

As previously stated the clinical recognition of choledocholithiasis involves a consideration of two groups of cases patients who have not been subjected to cholecystectomy and those whose gallbladders have been removed In the first group diagnosis is at best an uncertain matter since either calculous or noncalculous cholecystic disease can under certain circumstances produce practically all of the symptoms of stone in the common duct including jaundice Statistically it would not be difficult to show differences in the symptoms observed in patients with stone in the common duct and calculous cholecystic disease and those with the latter condition alone but in the individual case a definite distinction cannot always be made Unusually severe colics intermittent hepatic fever of Charcot repeated episodes of jaundice which are slow to clear and rarely, the presence of calculous shadows outside the gall bladder area in films made at this region after the giving of Graham s dye tetraiodophthalein sodium may give a clue to the diagnosis In known

calculous cholecystitis the absence of jaundice may give a false assurance as to the patency of the common duct and not infrequently the surgeon discovers sizeable stones in the ducts of patients who give no history of icterus

Since there are no absolutely reliable signs of choledocholithiasis in patients whose gallbladders have not been removed surgeons have stressed the necessity of careful palpation of the common duct in every case in which the extrahepatic biliary passage is subjected to surgical procedure It is the accepted practice to explore the duct with scoops if it is dilated or if there is an authentic history of jaundice with the result that an increasing percentage of stones in the common duct are being found and removed That there is still room for improvement in this direction is shown by the figures given by Judd and Marshall[7] in their cases about a fourth of the patients had had previous operations on the gallbladder most often cholecystostomy at which time stones in the common duct were almost certainly present and were overlooked In their group of 160 cases in which there were stones in the ampulla[8] 45 per cent of the patients had one or more previous unsuccessful operations on the biliary passages and 17 per cent had persistent biliary fistulas at the time of examination

When the gallbladder has been removed previously the problem of determining the presence of stone in the common duct is somewhat simplified but still it is not always an easy matter A history of stones being found at the previous operation is important noncalculous cholecystic disease or cholesterosis are not often accompanied or followed by calculi in the common duct Following cholecystectomies for stone however the occurrence of biliary colic chills fever and jaundice is strongly suggestive if not diagnostic of the presence of stones Unfortunately not more than 75 per cent of cases are characterized by such definite symptoms and analyses of large groups of cases show that in the remaining 25 per cent symptoms are sufficiently irregular to compel one to alter the usual diagnostic criteria and particularly to be liberal in one s interpretation of what constitutes a biliary colic or its equivalent The most common symptom of stone in the common duct is that of flatulent indigestion which persists after cholecystectomy and is aggravated by coarse or heavy foods Biliary colic in typical location and of sufficient severity to require morphine for relief is absent in about o per cent of the cases in these cases it may be replaced by episodes of aching epigastric or lumbar pain by pain of a colicky type in the left upper quadrant of the abdomen or by vague periodic digestive disturbances of a moderately painful nature From 2 to 5 per cent of patients with residual stone in the common duct have no pain of any kind[79] although obstruction of a sufficient degree to cause jaundice may have been present Not infrequently jaundice may develop without pain colics appearing at various intervals after the onset of

the jaundice Sometimes this sequence is reversed, and painless jaundice may come on long after an episode of colic Curiously enough a considerable number of patients have never been visibly jaundiced, or at least cannot give a good account of it, although they may have had typical biliary colics Chills and fever with mild epigastric distress may be the only symptoms, but many patients have no fever at any time Under these circumstances it is impossible to depend on fever as an index to the presence of suppuration in the bile passages, since there may be fever without suppuration and suppuration without fever In a few cases reflex cyclic vomiting may be the principal complaint and pain jaundice and fever a minor part of the picture In short, it is difficult to establish a history suggesting the presence of stone in the common duct in a substantial percentage of cases, whether the gallbladder remains in situ or has been previously removed

Physical Signs and Laboratory Data of Choledocholithiasis

Under this heading both cholecystectomized and non cholecystectomized individuals may be considered together There are no physical signs pathognomic of stone in the common duct Visible icterus is the most common finding it is rarely deep or persistent, and the skin seldom assumes the greenish hue seen in cases of malignant obstruction Pruritus and factitious dermatitis likewise are less frequent than in the last named condition Xanthomatous skin lesions about the eyelids, probably associated with hypercholesterolemia, have been emphasized but are not of particular importance The liver may be enlarged and tender, particularly after an attack of colic, and localized tenderness is often noted in the right hypochondrium and along the lower ribs posteriorly Splenic enlargement is not common except in neglected cases with advanced hepatic damage in fact splenomegaly when present, is a fairly certain sign of biliary cirrhosis The stools may be acholic for short periods but as a rule biliary obstruction is not complete or permanent and duodenal intubation will produce a good flow of bile, at least if repeated over a period of a few days In Weir s [73] series partial patency of the bile passages was noted in 90 per cent, and the serum bilirubin averaged less than 10 mg per 100 c c in 70 per cent of cases Both the color of the skin and the levels of bilirubin show marked fluctuation from day to day, the variation being much greater than that noted in jaundice from neoplastic obstruction or from parenchymatous hepatic damage In a few cases of painless jaundice from stone in the common duct a correct diagnosis has been made on this basis alone Studies of hepatic function reveal signs of injury to the liver, but seldom in the degree which commonly results from acquired benign stricture

Diagnosis and Treatment of Choledocholithiasis

From the foregoing it is apparent that stones in the common duct can produce syndromes simulating almost all of the various types of hepatic and biliary disease associated with jaundice and also that since stones may be present in the duct without jaundice a variety of other painful abdominal disorders may be simulated It must again be emphasized that about 25 per cent *of all cases of stone in the common duct are atypical in respect to some* or all of the usual clinical manifestations and for this reason many individuals carry such stones for years without their presence being detected In the presence of jaundice it is important to remember that primary hepatic disease or pancreatic neoplasms are the principal sources of error and that in cases without jaundice but with biliary colic or its equivalent the so-called post cholecystectomy syndrome is the principal stumbling block If jaundice is present the question of patency of the bile passages is the important point to decide If pain is the only symptom conditions mentioned in the differential diagnosis of cholecystic disease are to be reviewed

In general the diagnosis of stone in the common ducts of patients who have or who have not previously undergone cholecystectomy can at best be only presumptive unless jaundice supervenes in cases in which operation has been performed a history of stones in the gallbladder of prolonged post operative biliary drainage and of persistent dyspepsia may arouse suspicion. It is also a well established fact that episodes of acute abdominal pain which make an appearance years after successful cholecystectomy are very likely to be caused by stone and patients who suffer in this way should be subjected to careful observation following such attacks Subclinical degrees of jaundice following atypical episodes of abdominal pain may be detected by determinations of serum bilirubin and evidence of great diagnostic value may be secured in this way Leukocytosis and changes in the blood suggesting infection may be helpful and rarely the finding of calcium bilirubinate crystals in the duodenal contents also leads to a diagnosis Roentgenographic studies are rarely helpful once cholecystectomy has been performed

The hepatic complications that can be produced by stone in the common duct must not be forgotten in diagnosis There are on record a number of cases of supposed biliary cirrhosis or chronic hepatitis in which stones were finally shown to be the primary cause of the symptoms in others stones have first made their presence known by the production of severe or fatal suppurative cholangeitis Surgeons have learned generally that a high threshold of suspicion is essential and that the interests of the patient are best served by proceeding with exploration of the bile ducts rather than waiting until an unquestioned diagnosis can be established by other means

Once the diagnosis of stone in the common duct is established, or suspected treatment obviously must be surgical. Many unsuspected stones often will be detected by the experienced surgeon at the time of cholecystectomy, and he will explore the duct if it is dilated if pancreatitis is present, or if there is gross evidence of hepatitis or cholangeitis. If there have been recurrent or intractable symptoms, however atypical following previous operations on the bile passages the possibility of stone in the common duct will often lead the surgeon to consider choledochostomy. In most instances the duct may be opened in its supraduodenal portion, and the stone or stones removed by scoops. A transduodenal approach rarely is necessary except for the removal of the occasional stone which is tightly impacted in the ampulla. If, as is so frequently the case there is evidence of hepatitis or cholangeitis, drainage by T tube usually is maintained for a long period following the removal of stones, in order to eradicate infection in the ducts and parietal sacculi. Before the tube is removed the ducts may, and perhaps always should, be injected with a radiopaque oil and roentgenograms should be made so that their degree of patency can be ascertained. This procedure may save subsequent embarrassment by revealing either remaining stones in the ducts or signs of chronic pancreatitis and partial obstruction at the ampulla.

Parasitic Invasion of the Bile Ducts

Parasitic affections of the bile ducts while chiefly of academic interest to physicians in temperate climates are matters of considerable importance in other quarters of the globe. An increasingly large number of such cases is being reported from Russia, Egypt, Japan and Australia, and reports of native North American cases are appearing from time to time[80, 81]. Finkelstein[8] writing from Baku recently has reviewed the subject and has stated that in 530 operations on the bile passages he encountered parasites on 21 occasions. Mamikonoff[83] working in the Caucasus found 6 examples of parasitic invasion in 222 similar operations. The common invaders are ascaris lumbricoides echinococci and various species of liver fluke (distomiasis).

Ascariasis — Cirges[84] in describing the symptoms of ascariasis as seen in Egypt where the condition is common stated that in many cases there are definite symptoms of biliary involvement. The worm is an occasional invader of the common duct and at operation has been found in this situation repeatedly. At Perthes's Clinic in Tubingen there were said to be 16 cases of ascariasis in the bile ducts during the war years: poor sanitation and the eating of uncooked vegetables appeared to be responsible. Ascaris rarely reaches the gallbladder or hepatic ducts although Power and Johnston[85]

collected 7 cases from the literature in which the gallbladder was affected Women are said to be affected more often than men The condition is commonly associated with gallstones and it has been suggested[56] that the dilatation of the extrahepatic biliary passages associated with the presence of stones may favor invasion by the worm There are cases on record in which the ova or fragments of the worm itself appear to have formed nuclei for stones Two types of symptoms have been described those characterized by stormy onset evidence of acute obstruction of the common duct and empyema of the gall bladder and the more chronic type associated with the presence of gallstones In the latter ascaris seems to be an incidental invader

Since the clinical symptoms are not at all characteristic diagnosis is seldom made except at operation A history of infestation with worms may be important An increase in pain and in the depth of jaundice after the use of anti helminthics has been said to be diagnostic In some instances there has been no visible icterus even following severe biliary colic and in such cases it has been assumed that the presence of worms served to dilate the bile passages The finding of parasites or ova in the stools is essential for correct diagnosis it may sometimes be possible to demonstrate ova in the duodenal contents If there is evidence of obstruction to biliary flow treatment is primarily surgical although in occasional cases[57] the worm may be passed after vigorous treatment with santonin The long continued presence of parasites in the ducts leads to ascending biliary infection with suppurative cholangeitis and hepatic abscesses

Echinococcosis — Cysts of the liver caused by echinococci may involve the biliary passages in one of three ways by direct extension into the gall bladder by rupture into the intrahepatic ducts and by external pressure from the cystic mass Under the two first mentioned conditions the common duct may become occluded by daughter cysts From 5 to 10 per cent of echinococcic cysts in the liver are said to perforate ultimately into the biliary passages Sabadini[58] cited a long series of cases in which this accident had occurred. The usual result is biliary stasis and ascending cholangeitis but there are cases on record in which the common duct ruptured into the peritoneal cavity following invasion by daughter cysts As is the case with ascaris infection the condition frequently is associated with the presence of gallstones To carry the comparison further there seem to be two types of cases one with an acute onset of jaundice fever and signs of biliary obstruction and the chronic type in which jaundice develops slowly often because of compression of the ducts

Diagnosis is difficult it may be suggested by the finding of cysts in the vomitus or stools of a patient with an enlarged cystic liver and jaundice A positive complement fixation test or the demonstration of sensitivity to

echinococcic antigen injected intradermally may corroborate the diagnosis Eosinophilia is not often present [59] Treatment is entirely surgical and is directed primarily toward restoring the patency of the biliary passages The cyst in the liver may also be drained or marsupialized Systemic treatment is ineffective

Distomiasis — Liver flukes have been known occasionally to occlude the biliary passages in the various types of hepatic distomiasis Stiles[290] recorded six different varieties which may invade the liver and bile ducts The oriental liver fluke *Clonorchis sinensis*, is the most common offender It is acquired by contact with domestic animals and through eating raw fish Clinically the condition in its advanced stage is characterized by diarrhea, which may often be bloody, by a large tender liver and by anemia Jaundice, fever and ascites indicate the development of cholangeitis and hepatitis The disease is a very chronic one and is characterized by numerous remissions and relapses The Siberian variety of liver fluke *Opisthorchis felineus*, by its invasion of the bile ducts eventually leads to chronic proliferative cholangeitis and cirrhosis A somewhat similar disease, also due to infestation with flukes, is encountered in India Another variety, *Dicrocœlium lanceatum* is only a chance invader of man and of little clinical significance *Fasciola hepatica* is a rare invader of the bile passages, although Adams[291] found this fluke in an acutely inflamed gallbladder

A distinction should be made between the symptoms of true hepatic distomiasis and those produced by the presence of flukes in the common duct without extensive hepatic invasion Finkelstein [8] cited numerous cases from the recent literature in which flukes of various species had been found in the bile passages and had been removed surgically The condition in most of the cases mentioned by him simulated acute cholecystic disease or cholelithiasis, the characteristic symptoms of extensive hepatic involvement were absent Whether or not the surgical removal of flukes from the bile ducts prevents the development of further injury to the liver is not stated Diagnosis depends on the demonstration of the parasites or their ova in the stools, and it is not often made until the stage of extensive invasion of the liver is reached None of the surgical types have been recognized preoperatively Systemic treatment is ineffective

Other Parasites — There are other parasites which have been found in the bile passages but these are encountered only infrequently and are therefore of little importance *Giardia lamblia* which is commonly found in the duodenal contents, is probably not pathogenic although numerous authorities feel that it may cause symptoms suggestive of cholecystitis *Coccidia*, which are common in the livers of rabbits have rarely been found in man although Podwyssozki [3?] mentioned four cases apparently diagnosed from specimens at

necropsy Benedict[93] found a specimen of *Tænia saginata* measuring 310 cm in a gallbladder containing stones apparently the only case of this type of infestation on record

Tumors of the Bile Ducts

Benign Tumors of Bile Ducts

Benign papillomas have been found at various points in the extrahepatic biliary passages but they are encountered much less frequently in the ducts themselves than in the gallbladder Marshall[294] has reported a case in which a papilloma 4 mm in diameter obstructed the cystic duct and produced marked distention of the gallbladder Papillomas found in the common duct in association with choledochus cysts may be mentioned they may be primary or secondary to inflammatory processes Lipoma fibroma xanthoma and adenoma have been reported in a few cases the last named may be multiple and cystic and in some cases appear to originate from the epithelium of the bile ducts Such cystic adenomas are most frequently located within the substance of the liver and are described under the heading of cysts of that organ W J Mayo[39] has described two cases of adenofibroma of the stump of the cystic duct following cholecystectomy in both cases the tumors were closely attached to the common duct and produced obstruction by compression with intermittent colic and jaundice In each case resection of the tumor was possible and resulted in cure Comfort and Walters[96] recently have reported an example of neuroma of the cystic and common ducts which was successfully resected the patient being well three years later In their case the symptoms simulated those produced by stone in the common duct Because of the rarity of benign tumors in the bile passages and the absence of any characteristic signs or symptoms diagnosis is not possible except at the time of surgical exploration

Malignant Tumors of Bile Ducts

Occlusion of the biliary passages by neoplastic processes occurs most frequently as a result of carcinoma in adjacent organs notably the head of the pancreas although the stomach duodenum or adjacent lymph nodes may be the site of the original lesion Intrinsic carcinoma of the ducts themselves is considerably less common although several large series of cases have been reported[196, 94, 97] In contrast to the predominance of females affected by carcinoma of the gallbladder, males are predisposed to cancer of the ducts the sex ratio being almost 2 1 In carcinoma of the ampulla the predominance

of males is even more striking 14 of Marshall's[94] 15 patients being men In about three fourths of the cases the patients are past the age of fifty years No definite etiologic factors are recognized but it is of interest to note that in about one half of the cases recently reported either gallstones or less frequently, noncalculous cholecystic disease was present The association of stone and carcinoma is not as high in cases of carcinoma of the ducts as in cases of primary carcinoma of the gallbladder in which stones are found in practically every case

Pathology of Malignant Tumors of Bile Ducts — Nearly all of the intrinsic lesions of the ducts are carcinomas, columnar cell types predominating over those composed of spheroidal cells A high grade of malignancy is the rule, Judd and Gray[93] reported malignancy of grade 3 or more (Broders classification) in 65 per cent of their cases Papillomatous growths comprise only a small percentage of the total, and these are most commonly observed at the ampulla The remainder are largely infiltrating in type[93] and form hard, whitish localized strictures which may involve all of the coats of the duct and project into the lumen Considerable portions of the duct may be involved, and the growth may extend along the ducts into the substance of the liver By extension through the wall of the duct adjacent tissues, lymph nodes and organs may be involved in general however secondary malignant deposits are not conspicuous since the obstructive jaundice produced by the primary lesions usually proves fatal before metastasis can occur

The most frequent *situation* of the primary lesion appears to be the juncture of the cystic hepatic and common ducts here the growth may involve one two or all of these structures The ampulla is the next commonest site, and the hepatic ducts are third in order of frequency Involvement of the cystic duct alone is relatively uncommon Marshall[94] reported 5 cases of carcinoma in this location all of which as might be expected were associated with cholecystic disease When metastatic lesions are present the liver is the organ most often involved The hepatic changes produced by biliary stasis are a striking feature of tumors of the ducts the liver usually is enlarged bile-stained and on section shows extreme hydrohepatosis often with white bile in the ducts Periportal fibrotic changes and even obstructive cirrhosis are occasionally noted in cases of long standing and occasionally a terminal suppurative cholangeitis is found In rare cases tumors of one hepatic duct may produce obstructive biliary cirrhosis involving one lobe of the liver, under these circumstances jaundice does not appear In lesions of the ampulla the pancreatic ducts may be involved with development of chronic fibrous or hemorrhagic pancreatitis and exceptionally pancreatic insufficiency

Symptoms and Signs of Malignant Tumors of Bile Ducts — The symptom obviously will vary with the situation of the tumor and the presence of asso-

ciated disease of the gallbladder The clinical picture usually is that of a progressively increasing obstructive jaundice In Marshall's[94] series jaundice was absent only in the cases in which there was involvement of the cystic duct alone and in one case in which the patient previously had undergone cholecystenterostomy The onset is as a rule painless but as the condition advances pain may become severe definite biliary colics may be complained of or there will be dull constant discomfort in the epigastrium or right hypochondrium often being projected to the back The frequent association of cholelithiasis and cholecystitic disease in some cases introduces the element of infection but chills and fever are not commonly observed Clinical features suggesting infection appear to be more common when the primary growth arises in the ampulla Loss of weight and wasting are extreme as the condition progresses and pruritus is a distressing and often uncontrollable symptom About a third of the patients suffer from diarrhea and various symptoms referable to reflex motor disturbances of the stomach and duodenum are common especially in the later stages Profuse gastrointestinal bleeding may occur chiefly in association with ulcerating papillomatous lesions of the ampulla late in the disease a hemorrhagic tendency induced by prolonged obstructive jaundice may cause bleeding from the skin and mucous surfaces

On examination of the patient the most common findings are cachexia a deep greenish hued jaundice a palpably enlarged liver and a factitious dermatitis from pruritus and constant scratching An enlarged gallbladder is not commonly encountered but may be noted in cases of tumor involving the cystic or common duct Petechial and subcutaneous hemorrhages usually are a terminal feature and hepatic coma may develop shortly after the hemorrhagic tendency becomes manifest

Laboratory data in these cases occasionally may bring out some interesting information Anemia is not a conspicuous feature and when it is present it may signify occult bleeding from an ulcerating ampullary lesion The stools while usually acholic at times show traces of bile and duodenal intubation will in about 25 per cent of cases result in a small showing of bile pigment Gross blood in the duodenal contents is commonly found and when present is strong evidence of the presence of a neoplasm at or near the papilla of Vater

In a majority of the cases which I have observed a high fixed serum bilirubinemia is the rule in perhaps a fourth of the cases[294] slight variations in the depth of jaundice can be shown by determinations of serum bilirubin and these variations correspond with periods when the obstruction is temporarily relieved and bile appears in the stools or duodenal contents For obvious reasons individuals showing such variations in the degree of obstruction pursue a somewhat less rapid downward course it has been noted

that chronicity and intermittency in these cases usually indicate the presence of associated cholelithiasis

Liver functional studies in a few, proved advanced cases have indicated the presence of extreme hepatic damage as could be predicted from the marked hydrohepatosis present Prolongation of the coagulation time is a common finding, and the tendency to bleed is likely to increase in spite of any treatment

Diagnosis of Malignant Tumors of Bile Ducts —It is rarely possible to diagnose a primary malignant tumor of the bile ducts during life, the symptoms and signs being virtually indistinguishable from those produced by carcinoma of the head of the pancreas Complete or virtually complete biliary obstruction, deep and constant jaundice cachexia and a symmetrically enlarged and firm liver are findings common to all forms of malignancy that obstruct the biliary passages Usually it is possible to arrive at a diagnosis of neoplastic obstruction but beyond this point it is difficult if not impossible, to proceed The important thing in diagnosis is exclusion of jaundice resulting from parenchymatous hepatic disease, a point which usually, but not invariably, is differentiated by the patency of the bile passages that can be demonstrated sooner or later in the latter condition Splenomegaly is not uncommon in intrahepatic types of jaundice but it is rare in malignant obstruction, likewise, a positive galactose test may be indicative of jaundice caused by primary hepatic damage, and low values for blood cholesterol and cholesterol esters have somewhat the same significance If jaundice resulting from primary hepatic disease can be excluded an exact diagnosis of the cause of biliary obstruction is not of great practical significance exploration should be carried out, if and when, the condition of the patient permits

Course Prognosis and Treatment of Malignant Tumors of Bile Ducts —After jaundice makes its appearance the course of the disease if untreated, rarely exceeds six months hemorrhage and hepatic insufficiency being the common terminal events In the exceptional case the tumor may ulcerate sufficiently to relieve partially the obstruction and to permit a flow of bile, the jaundice may then clear temporarily and life thus may be prolonged Without surgical intervention the prognosis is absolutely bad While operative mortality is high 33 per cent in Renshaw's[300] series generally it is supposed that obstructive jaundice will of itself produce a fatal outcome long before a potentially resectable tumor of the bile ducts has passed the stage of operability

Tumors of the hepatic ducts practically never are operable in one case[298] Judd scooped out a portion of the tumor and performed choledochostomy with a good temporary result Tumors of the cystic duct occasionally are removable, those of the junction of the cystic and common duct and of the common duct

only, alone rarely so In the latter groups cholecystenterostomy often is possible if the cystic duct is patent and this operation may give relief for periods of a year or more For lesions confined to the ampulla radical transduodenal resection sometimes is feasible and a number of cases are on record in which the patient was well months or years after radical removal of the growth by this means

Hemorrhage is the principal cause of operative fatalities infection in the form of suppurative cholangeitis or peritonitis also figures heavily in the cause of death In Marshall s[94] series of 45 patients 26 survived operation for an average period of seventeen months and 3 were living five sixteen and twenty eight months after operation

Extrinsic Tumors (Malignant and Benign) Occluding the Biliary Passages

As was stated in an earlier paragraph carcinoma of the pancreas is the commonest cause of compression of the bile ducts by extrinsic processes This condition is discussed under the head of pancreatic disease (Vol III Chapt VIII) and in the section on jaundice (Vol III Chapt V) and will not be considered in detail here The clinical picture virtually is identical with that produced by intrinsic tumors of the ducts a condition much less frequently encountered in practice One differentiating feature may be mentioned a distended gallbladder is common in cases of pancreatic carcinoma and rare in association with tumors of the ducts Frequently it is impossible for either the surgeon or the pathologist to determine the primary source of a tumor in the region of the termination of the common duct as Outerbridge[97] pointed out there are six possible sites of origin in this very small region (1) the ampulla of Vater (2) the common duct itself (3) the termination of Wirsung s duct (4) the glandular structure at the head of the pancreas (5) the duodenal mucous membrane and (6) Brunner s glands in the duodenal mucosa Clinically all may be considered under one heading since the symptoms are similar Pancreatic involvement occasionally may be indicated by the presence of pancreatic diarrhea glycosuria or both curiously enough these phenomena are not as frequently encountered as might be expected The indications for treatment of obstructive lesions from extrinsic compression of the bile ducts are clear surgical exploration should be attempted if the patient s condition warrants it with the hope that a short circuiting operation such as cholecystgastrostomy can be performed

Among the rarer lesions obstructing the common bile duct by compression may be mentioned (1) stones in the stump of the cystic duct after cholecystectomy (2) chronic pancreatitis (3) pancreatic cysts or adenomas (4) tuberculous glands in the portal fissure, (5) Hodgkin s disease with local glandular

enlargement (6) tumors of the kidney, stomach, duodenum, or colon with extension into the region of the common duct, (7) gummas and other granulomatous lesions, (8) retroperitoneal tumors, and (9) aneurysms especially of the hepatic artery I have seen one remarkable case in which a foreign body granuloma, produced by gauze packing used years before in controlling bleeding from a stab wound obstructed the duct Diagnosis of most of the aforementioned conditions is largely by inference and exclusion and can be established clinically only infrequently For a fuller consideration of these and related types of obstructive lesions the reader is referred to the chapter on jaundice

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CHAPTER VIII

DISEASES OF THE PANCREAS

By JOSEPH H. PRATT

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INTRODUCTION

Disease of the pancreas often is difficult to recognize clinically Knowledge of the physiology of the gland is extensive as is that of its pathological anatomy but pathological physiology and differential diagnosis lag far behind This is due mainly to three things (1) Its position in the posterior part of the abdominal cavity behind stomach and intestines makes it usually inaccessible to the palpating hand even when enlarged (2) Its close relation topographically and functionally with stomach duodenum and biliary tract causes symptoms produced by disease of the pancreas to simulate those of these neighboring organs (3) Definite disturbance of its external digestive functions do not appear until practically all the pancreatic juice is absent from the intestine A bit of pancreas one centimeter in size connected with the main duct is sufficient in the dog to insure normal digestion and absorption The same is true of the internal function By tying the ducts the gland may be reduced to one tenth or less of the normal size and be largely converted into dense fibrous tissue without diabetes resulting

Recent studies have shown that slight lesions of the pancreas are common Rich and Duff (1936) in an histological examination of the routine autopsy material at the Johns Hopkins Hospital have found repeatedly metaplasia of the epithelium of the branches of the pancreatic duct system associated with fat necrosis or focal hemorrhages This finding supports a statement of Goldschmidt made after examining all sections of the pancreas in Askanazy s Institute for a long period of time that 'histological changes in the pancreas are almost incredibly frequent (Katsch and Brinck 1938) Calculi have been regarded as of very rare occurrence yet routine x ray examination of 542 pancreases followed by microscopic examination revealed concretions varying in size from the

head of a pin to that of a hazel nut in 28 or about 5 per cent of the cases (Ludin 1938)

Evidence also is accumulating from combined clinical and laboratory studies that attacks of epigastric pain especially those occurring in association with biliary disease are due not uncommonly to mild acute lesions of the pancreas

PHYSIOLOGY

The ferments found in the pancreatic juice are the specific products of the pancreatic secretion They digest fat carbohydrates and protein so efficiently that when other digestive organs do not function properly as for example when as in achylia the stomach fails to produce pepsin digestion and absorption of foodstuff still are maintained within normal limits

The ferments of the pancreas are most active when the reaction is neutral or slightly alkaline The optimum reaction is dependent on the substrate Trypsin for example digests gelatin best at a pH 8 9 casein and peptone at a pH 8 0

The pancreas secretes also an alkali in the form of bicarbonate This is needed to neutralize the gastric juice The titration alkalinity of 100 c c of pancreatic juice corresponds to 100 c c of n 10 alkali and it will neutralize about an equal amount of gastric juice In the resting state the alkalinity is distinctly less

Pancreatic trypsin consists of a mixture of different ferments the most important of which is a proteinase This ferment acts on native protein as does the pepsin of the gastric juice but it breaks down the protein into simpler bodies than does pepsin Trypsin is secreted in an inactive state as a proenzyme trypsinogen which under normal conditions does not become activated until it comes into contact with the mucous membrane of the duodenum where it is converted into trypsin by enterokinase The activation of the pancreatic juice is an autocatalytic process When once a small amount of trypsin has been formed the activation of the trypsinogen proceeds at an accelerated rate

Steapsin the lipase of the pancreatic juice splits the neutral fat into glycerol and fatty acids The latter in the intestine are converted largely into soaps The action of lipase is dependent on the composition and colloidal state of the material in which it is present A number of substances strongly increase its activity The most important of these is bile the activating action of which is due chiefly to its content of glycocholic and taurocholic acids Calcium salts and protein substances also increase lipase activity

Pancreatic amylase or diastase acts on starch and glycogen to form maltose This is a disaccharid and is not absorbed as such from the intestine The mucous membrane of the intestine produces a maltase which by hydrolysis converts the maltose molecule into two glucose molecules

The dependence of the digestive function of the pancreas on the activity of the intestinal mucous membrane is indicated not only by the formation of maltase the action of which forms a sugar that can be absorbed and enterokinase that activates trypsinogen but it also forms the hormone that acts on the acinar tissue of the pancreas secretin This substance has been produced recently in crystalline form It is a specific basic peptid and can be sterilized without loss of activity The commercial preparation pankreotest has about a fifth of the activity of the crystalline hormone The intravenous injection of 4 mgm of pankreotest produces about 250 c c of pancreatic juice The abundant secretion usually begins to flow within 1 minute after the injection into a vein of the arm The volume of secretion usually reaches its maximum within ten minutes the peak being followed by a rather slow decline There is a large amount of trypsin and diastase excreted during the first ten minutes and a rapid rise in the concentration of bicarbonate Secretin also stimulates the flow of bile which is taken up by the gall bladder so effectively that no bile or only a trace appears in the duodenal contents (Ägren and Lagerlof 1936)

Pathological Physiology

Effect of Excluding Pancreatic Juice from the Intestine on the Absorption of Food

It was long held that the pancreatic juice was not essential to digestion although as early as 1856 Claude Bernard presented evidence from animal experiments that the pancreatic juice was of great importance in digestion and in the absorption of fat by the intestine The evidence was not conclusive and a number of later experimenters found good absorption of fat and nitrogen after tying the pancreatic ducts Their results can be explained either by the escape of pancreatic juice into the intestine through the formation of sinuses in the necrotic tissue about the ligatures or to the failure of the operator to tie all the ducts The author of this chapter and his associates (1909) have shown that in dogs there is a great diminution in the absorption of nitrogen and fat when the pancreatic juice was excluded from the intestine

There is no doubt that dogs when deprived of their pancreatic juice vary greatly in their power to absorb fat and nitrogen and furthermore that there is a great variation in the same animal on the same diet at different times (Handelsman Golden and Pratt 1934) It should be emphasized however that all dogs without pancreatic juice always show a considerable disturbance in the absorption of fat and nitrogen Clinical observations indicate that these statements are true for humans as well as animals

A completely depancreatized dog always loses in the feces much of the fat and nitrogen of the food but McClure Vincent and Pratt (1917) found that sometimes considerable fat and nitrogen are absorbed In one experiment no less than forty five per cent of the fat of the food was utilized

Signs of Absent External Pancreatic Secretion

Interference with the flow of pancreatic juice into the intestine from obstruction of the ducts has been observed repeatedly in chronic disease of the pancreas It is very rare in acute disease In cancer of the pancreas evidence of diminished or absent pancreatic secretion gained from a study of the feces is of great importance in diagnosis

Diarrhea is an important symptom in obstruction of the pancreatic ducts from any cause The passage of two or three voluminous unformed stools daily on a diet rich in fat and meat without signs of intestinal disease such as blood or mucus is suggestive of severe pancreatic disease The stools rarely are watery In extreme atrophy of the intestine such as occurs in sprue and in tuberculous disease of the mesenteric lymph nodes which prevents the absorption of fat a type of diarrhea is seen resembling closely that of pancreatic disease On the other hand in some cases of obstruction of the ducts the stools may be formed for a time and not especially bulky Much depends on the diet the patient is taking The bulk and light color of the feces are the most important signs of pancreatic disease brought out by naked eye examination If the amount of fat is large the stools become almost white As the stools in jaundice also are fatty it is often well to resort to Schmidt s corrosive sublimate test for bile pigment in order to make sure that the pale color of the stools is not due in part to absence of hydrobilirubin

Use of the intestinal diet of Schmidt (1915) is of great aid in the diagnosis of obstruction of the ducts in chronic pancreatic disease The diet contains enough fat and rare meat to test the functional efficiency of the pancreas This standard test diet has enabled us to compare our

results with those obtained by Schmidt and other workers in this field As it appears in different papers variously modified yet bearing the name of the Schmidt diet it is important to state that the diet we used conformed exactly to instructions given by Schmidt as follows — *Mornings* 0 5 liter of milk with 50 gm zwieback *Forenoons* oatmeal gruel (40 gm rolled oats 10 gm butter 200 gm milk 300 gm water and 1 egg and salted to taste — strain) *Noon* 125 gm finely chopped roast beef (raw weight) lightly broiled *so that the interior remains uncooked* In addition 250 gm potato purée (made of 190 gm potato 100 gm milk and 10 gm butter salted to taste) *Afternoons* as mornings *Evenings* as forenoon

This daily diet contains according to Schmidt 102 gm protein 111 gm fat and 191 gm carbohydrates This yields 2 234 calories (computed from Koenig s tables) The average of 5 analyses made in our laboratory gave protein 102 gm fat 132 gm carbohydrates 180 gm with a caloric value of 2 324

This diet is given for three days To mark off the stools 0 3 gm of carmine is taken with the first meal The feeding period ended we give on the following morning 1 gram of wood charcoal with a breakfast consisting wholly of milk The charcoal is given best in the form of an emulsion (Rx Carbo vegetab 15 gm mucilago gummi arab, 15 gm, aq menthæ pip 60 c c) Of this 3 teaspoonfuls are taken After the beginning of the test diet the first stool colored red with carmine is saved and collections continued until charcoal appears The first stool colored with charcoal is rejected The feces of a normal person taking the Schmidt diet has a uniform consistence and a light brown color

Much information often may be gained from the weight of the dried stools With pancreatic juice absent from the intestine not only are the stools bulky but the dried residue weighs more than that obtained in any other condition In a series of six healthy persons placed on the test diet for three days Schmidt found the average weight of the dried feces to be 54 3 grams for the three day period The maximum was 62 grams and the minimum 45 grams In my own experience the weight of the dried stools with the patient on the Schmidt diet has been of value in diagnosis as Table I shows

It is seen from these figures that in every instance in which the dried stools weighed more than 300 grams there was complete obstruction of the pancreatic ducts

Steatorrhea — When the pancreatic ducts are obstructed, the feces usually are very light in color due to the presence of fat If the amount of fat is large the stools often are almost white The passage of butter

TABLE I

WEIGHTS OF DRIED FECES OF PATIENTS ON THE SCHMIDT DIET
(Three day Period)

Case	Name	Disease	Total weight of dried feces gm
1	Mr J	Normal	45 0
	Mr Ba	Biliary cirrhosis with slight icterus	31 0
3	Mr B	Chronic pancreatitis (?) (period with pancreatic ferments added to diet)	[illegible]
4	Miss M	Steatorrhea of unknown origin	130 0
5	Mrs Ma	Obstructive jaundice	131 0
3	Mr B	Chronic pancreatitis (period without pancreatic ferments)	143 0
6	Mr C	Sprue	[illegible]
7	Mrs D	Chronic obstructive jaundice	[illegible]
8	Master N	Gee Thaysen's disease	[illegible]
9	Mrs W	Sprue	269 0
10	Prof G	Obstruction of common bile and pancreatic ducts (with pancreatic ferments)	355 0
10	Prof G	Obstruction of common bile and pancreatic ducts (without pancreatic ferments)	419 0
11	Mr Mc	Obstruction of pancreatic ducts	438 0
12	Mr F	Obstruction of common bile and pancreatic ducts	456 0
13	Miss K	Obstruction of common and pancreatic ducts	463 0

like masses usually to be found on the surface of the stool is pathognomonic of pancreatic disease These masses of pure fat formerly were thought to be made up of unsplit fat but it is now known that they may consist largely of fatty acids in the form of droplets If fat crystals are present in very large number they *may* give to the feces a metallic luster resembling that of aluminum paint

The association of free fat and undigested muscle fibers in the feces with pancreatic disease is undoubted In disease of no other organ has free fat been found in the feces When passed in an oily state it quickly hardens into butter like masses Cases with free fat in the stools have been reported rarely The number would be much larger if the feces in pancreatic disease were examined carefully Tileston (1911) observed macroscopic fat in five out of six cases in which the pancreatic ducts were obstructed In three the fat looked like butter in the other two it formed creamy masses He pointed out that the stools should be examined frequently while the patient is on a diet rich in fat and that the stools if formed should be cut with a knife as the fat masses sometime may be found in the interior when there is none upon the *surface* of the stool

In health on the Schmidt diet the average percentage of fat in the stools is 25 In long continued fasting as much as 36 per cent of the

dried stool has been found to be fat This fat as Hill and Bloor (1922) showed comes from the intestinal secretions In our experience 15 of 2 cases with grossly recognizable fatty stools contained over 50 per cent of fat Three of six cases with a fat content between 60 and 70 per cent were cancer of the pancreas Of five patients who had on the Schmidt diet over 70 per cent of fat in the dried stools two had obstruction of the common bile duct two sprue and only one cancer of the pancreas The highest percentage of fat 86 2 was in a case of sprue These figures show that the percentage of fat is of no value in the diagnosis of pancreatic disease

The determination of the amount of fat absorbed on a known diet yields results of value in diagnosis but not only requires the help of a chemist and special equipment but is very laborious and time consuming As a result not many figures are given in the literature The first exact studies of fat absorption in jaundice were made by Friedrich Muller (1887) In complete obstruction of the common bile duct he recovered between 55 and 79 per cent of the ingested fat in the stools Brugsch (1906) found on the average about 45 per cent unabsorbed in obstructive jaundice If the fat loss in jaundice is above 45 per cent one always should suspect the simultaneous involvement of the pancreas In a case of obstructive jaundice combined with occlusion of the pancreatic ducts a study made in my laboratory showed that 65 5 per cent of the fat in the Schmidt diet was excreted in the stools A second period on the same patient showed a loss of 66 2 per cent In another case of cancer of the pancreas with obstructive jaundice Spooner and Pratt (1912) found that 80 per cent of the fat of the food was not absorbed

The amount of fat excreted in sprue may equal that in pancreatic disease In a case of sprue with severe diarrhea Thaysen (1926) found 66 grams of fat in stools collected on a single day The average daily excretion of fat in his series of chronic pancreatic disease was 65 grams while in sprue the average was 36 grams In a patient of mine with occlusion of the pancreatic ducts the feces collected in one day contained 89 grams of fat

Studies in recent years have brought to light two important points in regard to steatorrhea First it is less common in cancer of the pancreas and in chronic pancreatitis than formerly was thought The entrance of even a small amount of pancreatic juice into the intestine is sufficient to digest fat and meat fibers Hence even if the main pancreatic duct is completely occluded the accessory duct provides enough pancreatic juice for digestion Second sprue in some clinics is a more frequent cause of fatty stools than pancreatic disease During a period of ten years ending

in 1938 no less than 24 cases of non tropical sprue were admitted to the medical clinic in Zurich and only 5 cases of steatorrhea of pancreatic origin during this time 6 cases of pancreatic cancer and 1 case of chronic pancreatitis without fat stools were observed (Hotz 1938)

After heating a bit of feces rich in fat with a few drops of 30 per cent acetic acid almost the entire field of the microscope is occupied by fat globules In cases where an increase of fat is not recognizable yet suspected a simple and satisfactory method is the following Place a small particle of feces on a microscopic slide add a drop of solution of Sudan III in acetic acid alcohol bring to the boiling point over a flame and observe under a cover slip All the fat will be melted and appear as red drops

Creatorrhea — The presence of *undigested muscle fibers in the stools is seen regularly on microscopic examination when the pancreatic juice is* excluded from the intestines Both the longitudinal and transverse striations are preserved and the bits of muscle fiber often have square or slightly rounded edges On a diet fairly rich in rare meat large numbers of muscle fibers are found often in pancreatic disease The feces of a healthy person on the Schmidt diet may show a few partly digested muscle fibers but usually they are changed into small oval yellowish bodies without visible striations In diarrhea usually only a small number of muscle fibers occur in the feces *but in exceptional cases they may be so numerous that a suspicion of pancreatic disease may be entertained falsely* In ordinary diarrhea the stools are watery while in pancreatic obstruction they are bulky and pultaceous In diarrhea the passage of food through the alimentary tract is shortened while the time is normal in pancreatic disease about twenty four hours This can be determined by giving a single dose of charcoal and noting the lapse of time before the charcoal can be detected in a stool on gross or microscopic examination In obstruction of the common bile duct and also in sprue creatorrhea is absent Rarely bits of muscle large enough to be recognized on naked eye examination are present in the feces *It is safe to assert that the constant finding of large numbers of undigested muscle fibers with a normal time of* passage of food through the intestine is diagnostic of pancreatic disease

Nitrogen Absorption as an Aid to Diagnosis — Chemical analyses show that the loss of nitrogen is great in the absence of pancreatic juice from the intestine After separating the pancreas from the duodenum and thus excluding all pancreatic external secretion Pratt Lamson and Marks (1909) found that a nitrogen loss in the feces was of constant occurrence and of high degree amounting to from 38.3 to 77.8 per cent of the nitrogen

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The usual dose of pankreon in cases of pancreatic obstruction is five to six grams daily and of pancreatin at least two to three grams daily divided into four or five doses

The raw pancreas probably is more effective than the prepared ferments It is essential that it be freshly obtained Calf s beef s or pig s pancreas may be used Mosenthal (1912) and Janeway served raw pancreas with mayonnaise dressing as a salad giving 150 grams daily In my experience raw pancreas is distasteful to patients and its use has to be abandoned soon However Mosenthal (1937) has reported the case of a patient who has been taking raw pancreas for eight years Whenever he omitted the pancreas the steatorrhea returned Bargen Bollman and Kepler (1936) claim they checked diarrhea of pancreatic origin by an extract of pancreatic juice administered in capsules

Disturbance of the Internal Secretion of the Pancreas

The association of diabetes or alimentary glycosuria with disease of the pancreas has been known for more than a century In a series of 29 cases of pancreatic disease with fatty stools collected from the literature by Fitz (1903) diabetes was present in 11 In dogs with chronic pancreatitis and atrophy resulting from tying the ducts I found that the tolerance for glucose always was reduced and in some instances markedly although diabetes did not result In a collection I made of 37 cases of pancreatic disease studied by functional methods spontaneous glycosuria occurred 6 times and alimentary glycosuria 4 times only 2 of the 10 cases were cancer It is important to make frequent examinations of the urine as transitory glycosuria is a symptom that is overlooked frequently

In recent years the importance of determining the amount of the blood sugar in the diagnosis of acute pancreatic necrosis has been demonstrated repeatedly Activated trypsin destroys insulin As the trypsin enters the blood stream it destroys insulin in the circulating blood As a result the blood sugar often is increased during the first hours of the disease According to Bernhard (1935) this occurs in half of the cases In Nordmann s experience it occurs in a much larger percentage Trasoff and Scarf (1937) found that hyperglycemia existed in 100 per cent of 10 cases examined The range was 190 mgm to 330 mgm As sugar usually is not excreted in the urine until a threshold value above 200 mgm is reached in the blood glycosuria occurs in only a portion of the cases in which hyperglycemia exists In recent studies not over 7 to 10 per cent of the cases had sugar in the urine

If a high blood sugar is not obtained at the first examination it is well

content of the food Recent studies in our laboratory show that while in dogs deprived of pancreatic digestion the fat loss can be largely prevented by changes in the diet a considerable nitrogen loss persists with all diets Our clinical observations show that this faulty absorption of nitrogen is of greater value in the recognition of pancreatic disease than is the faulty absorption of fat The average loss of nitrogen in the feces in pancreatic obstruction is about 40 per cent In one of our cases it reached 61 per cent In the other forms of steatorrhea studied the loss of fat to the body is not associated with so marked a loss of nitrogen In two of our cases of obstructive jaundice 93 and 92 per cent of the nitrogen of the Schmidt diet were utilized These figures are within normal limits The lower limit of normal is about 85 per cent

In sprue the nitrogen absorption may be little if at all disturbed In two cases of sprue on which we made studies with the patient on the Schmidt diet the utilization of nitrogen was 86 6 and 90 4 per cent In a third case on a milk diet the nitrogen absorption was 99 1 per cent, the highest we have ever seen

The percentage of nitrogen in the dried feces has proved of no value in diagnosis In 6 cases of cancer of the pancreas the percentage of nitrogen ranged from 1 7 to 8 0 Even the highest figure has no significance as Rubner found 8 3 per cent of nitrogen in the dried feces of a healthy subject fed on white bread

Although the percentage of nitrogen is of no value in diagnosis the total amount of nitrogen excreted daily is helpful because it is low in sprue and in obstructive jaundice and high in occlusion of the pancreatic ducts In a case of obstruction of the common duct we obtained a daily excretion of only 1 1 grams of nitrogen on the Schmidt diet in sprue 1 6 grams and 2 7 grams while in complete occlusion of the pancreatic ducts as much as 8 5 grams of nitrogen

Effect of Administering Pancreas — The use of fresh pancreas or pancreas preparations in diagnosis is of limited value as the effect in reducing a fatty diarrhea due to pancreatic duct obstruction may be slight or absent occasionally the stools become natural and the patient gains weight. When this occurs the evidence points to the pancreas as the seat of disease but it is not conclusive as the patient may be recovering from a non pancreatic fatty diarrhea at the time the test is made

As the HCl of the gastric juice destroys the ferments of the pancreas it is well to give large amounts of pankreon a combination of pancreatin with tannin as it is protected in the stomach but is dissolved by the dilute alkalies of the intestine If achylia gastrica exists and its association with pancreatic disease is frequent pancreatin alone may be used

that the diastase may fall to normal in both blood and urine within thirty six to forty eight hours of the onset and usually has returned to a normal level at the end of three or four days This important fact was pointed out first by Skoog (1930) and has been confirmed repeatedly Diastase is increased in the blood in uremia but not markedly so (Fitz 1915) as it is decreased in the urine in uremia there would be no confusion with the findings in pancreatic disease

The necrosis may be progressive and proceed to a fatal issue yet the diastase having dropped to normal fails to rise again Occasionally the diastase activity will remain increased for a week or more but this persistence of a positive test bears no relation to the extent of the pancreatic lesion

Diastase in the Urine — The examination of the urine for diastase is even more important than that of the blood in the diagnosis of acute pancreatic necrosis as it is found elevated more frequently McClure and Pratt (1917) determined the urine diastase in 22 normal men and found the maximum value to be 80 units measured by the original Wohlgemuth method and 200 units in a group of 108 hospital patients without signs of pancreatic disease Foged (1935) also in the urine of 100 normal men found values up to 200 units Simon Gubergritz and Kaczander (1931) have called attention to the lack of agreement between the diastase values in the blood serum and in the urine

Doberer (1937) analyzed the cases studied in Clairmont s surgical clinic in Zurich He states that the majority of their cases of acute pancreatic necrosis showed no increase in blood diastase although the urinary diastase almost always was increased The highest serum diastase value observed in that clinic in acute pancreatic necrosis was 256 units while the urine diastase at least at the beginning of the disease always showed very high values Bernhard and Kaczander probably are right in asserting that the determination of the urine diastase is sufficient Values in the urine of 256 units can be regarded as proof Doberer holds of the presence of a pancreatic lesion An increased diastase value is rare in cancer of the pancreas or in chronic pancreatitis When present it is probably always transitory and attributable to congestion or toxic influence The diastase value is said to be normal in both blood and urine in about 10 per cent of the cases of acute pancreatic necrosis even in the early stage of the disease

Methods of Diastase Determinations — Wohlgemuth s method especially with the improved technique described by Wohlgemuth in 1929 is entirely satisfactory for clinical use as the deviations from the normal in acute pancreatic disease are great.

to do a glucose tolerance test by Staub's method which is as follows give 20 grams of glucose per mouth at 7 A M and 20 grams more at 8 A M determine the blood sugar every half hour for three hours Loeffler (1938) demonstrated the value of this procedure In 5 cases of acute pancreatic necrosis the initial blood sugar was below 140 mgm per cent and in three of these 110 mgm or less Yet in all 5 cases an abnormal curve was obtained In 2 of these the blood sugar level rose above 200 mgm in the second or third hour

Demonstration of Pancreatic Ferments

Agren and Lagerlof (1936) in Sweden have devised a test of pancreatic function that promises to be of great value in the diagnosis of pancreatic disease This test is based on the discovery by Hammarsten and Ågren of a method of preparing secretin of such purity that it produces no untoward effect when injected into a vein The use of a special double tube permits the separate withdrawal of gastric and duodenal juice Numerous holes in the tubes make it possible to obtain practically all the secretion from stomach and duodenum Prior to the injection of secretin the duodenal contents are collected in 20 minute periods until a fasting value is obtained which varies between 0 and 25 c c Generally this basic value is reached in 20 to 40 minutes After the secretin injection the duodenal and gastric contents are collected in two ten minute and then twenty minute periods The volume and concentration of bicarbonate and bilirubin are determined in each sample of duodenal secretion The diastase and trypsin in an aliquot part of the assembled fractions are determined and the volume and hydrochloric acid content of the gastric fraction are measured

In convalescence from acute pancreatic necrosis Agren Lagerlof and Berglund (1936) found a diminution in diastase production It probably represents the mildest form of disturbed function detectable by the secretin test In a second type of deviation from the normal trypsin and diastase values both are diminished This finding is considered characteristic of a diminution of the mass of pancreatic tissue

Diastase in the Blood — Normally the blood has a slight diastase activity When the pancreatic ducts of the dog are tied there is a great increase in the diastase activity within a few hours This reaches its maximum usually within forty eight hours

In acute pancreatic necrosis there is likewise a striking increase in the diastase value and this has proved of great diagnostic importance It is present at the time the symptoms develop *It is not generally known*

meters of 1 per cent starch solution which will be converted into erythrodextrin by 1 c c of blood serum With this technique values between 4 and 64 are normal

More accurate than the Wohlgemuth test are some of the sugar reduction methods in which sodium chloride i used as an activator of the ferment and a satisfactory pH is employed The optimum for the blood diastase serum is 6 8 The methods of Somogyi (1938) Salter (1936) and Nørby (1936) can be recommended All of them are time consuming and require chemical skill and considerable equipment

Lipase in the Blood —Cherry and Crandall (1932) demonstrated that a lipase which hydrolizes olive oil normally not present appeared in the blood following the ligation of the pancreatic ducts of dogs The activity of the enzyme esterase normally present in the blood as measured by hydrolysis of ethyl butyrate or tributyrin did not show uniform increase in their experiments They devised a simple titration method for the determination of lipase in the blood serum using olive oil as a substrate Comfort (1937) using this method obtained elevated values in 20 out of 21 cases of acute pancreatic necro is examined within ten days after the onset of symptoms The upper limit of lipase activity in persons without pancreatic disease is given by him as about 1 5 c c in terms of 1 .0 *sodium hydroxide per 1 c c of serum although Cherry and Crandall* found that the serums of 40 of 46 patients did not reveal any trace of lipase splitting olive oil In acute pancreatic necro is a value as high as 10 2 c.c has been obtained The earlier in the disease the blood was examined the higher was the value Fourteen days or more after onset the serum lipase was normal The serum lipase value was elevated in 15 out of 41 cases or 36 per cent in cancer of the pancreas and in 60 per cent of those in which there was carcinoma of the ampulla of Vater

Other Metabolic Disturbances —In acute pancreatic necrosis there is marked destruction of protein with an increase of the non protein nitrogen of the blood Bernhard has observed a case in which it reached 250 mgm per cent There were pronounced uremic phenomena In 25 cases the non protein nitrogen was above 40 mgm per cent in 14 Toxic injury *to the kidney from the abnormal products of protein metaboli m* circulatory failure and dehydration all contribute to the elevation of the non protein nitrogen

In a case of pancreatic tumor reported by Bauer (1932) hypochloremic azotemia chloropenic uremia developed This condition has been observed by Adlersberg and Wachstein (1937) after experimental extirpation of the pancreas

The substrate is a 1 per cent solution of soluble starch (Kahlbaum) to which is added an equal amount of a buffer phosphate mixture (pH 7.2). The phosphate mixture is prepared according to Michaelis from primary and secondary phosphate solutions. Primary phosphate solution consists of 5 c.c. of a 3/1 normal phosphoric acid (1 mol in 1 liter of water) to which is added 5 c.c. of 1/1 normal sodium hydroxide and 5 c.c. of water. The secondary phosphate solution is composed of 5 c.c. of 3/1 normal phosphoric acid plus 10 c.c. of 1/1 normal sodium hydroxide. Take 5 c.c. of the primary and add 10 c.c. of the secondary phosphate solutions. This mixture has a pH of 7.2. For the urine diastase this gives the optimum reaction. To make up the starch solution place 60 to 70 c.c. of 1 per cent sodium chloride solution in a beaker; boil. Place 1 gram of Kahlbaum's soluble starch in a small vessel, stir up with some of the salt solution and pour in a thin stream into the boiling sodium chloride solution. Wash the vessel several times. After boiling and cooling make the volume of the solution up to 100 c.c. To prepare the diastase reagent take 10 c.c. of the 1 per cent starch solution and 10 c.c. of the phosphate mixture. Make up to 100 c.c. with 1 per cent or physiological sodium chloride solution. If the surface of this solution is covered with a thick layer of toluol, at least 10 c.c., it will keep indefinitely.

Into each of a series of 12 small test tubes 1 c.c. of a 1 per cent sodium chloride solution is pipetted. In each of the first two tubes is placed 1 c.c. of blood serum or neutralized urine and mixed well with the sodium chloride solution. From the second tube 1 c.c. is removed with a pipette and added to the third tube. In the same way the blood serum or urine is diluted further by removing 1 c.c. from each tube and adding it to the next lower in the series. Finally 2 c.c. of a buffered starch mixture (pH 7.2) are added to each tube. The tubes are then kept at 38° C. for thirty minutes. Then after rapid cooling a few drops of $\frac{N}{50}$ iodine solution are added to each tube. The partly digested starch now assumes a purple color, the completely digested starch a light yellow color. The end point is in the last tube that shows a purplish hue. The next lower dilution of serum yields a pure blue color. Let us suppose the end point is reached in the fourth tube. The diastase activity which was able to begin the digestion of starch in the dilution of serum present in this tube is calculated as follows:

$$\text{Diastase units} = 2^4 = 16 \frac{(38°)}{(30')}$$

The units expressing the diastatic value are the number of cubic centi-

(Head's zone) A needle is used by Katsch in marking out the area By tapping the skin or picking it up in folds tenderness of the deep tissue can be demonstrated Katsch (1938) in his latest publication on the subject fails to state the number or percentage of cases of acute pancreatic necro is in which he has found the typical pain or the Head zone of cutaneous hyperesthesia Loeffler in a recent study states that pain extending to the left was present in only one of five cases of acute pancreatic necrosis Hyperesthesia of the skin is present more frequently as a neurotic manifestation than as a result of visceral disease in the experience of the writer Severe persisting abdominal pain in the absence of any abnormality detectable by ordinary physical examination or by x ray may be the only evidence of cancer of the pancreas

Types of Acute Pancreatic Disease

It is important clinically to divide the cases into three groups although usually they are different manifestations of the same underlying disease

1 Acute pancreatic edema
2 Acute pancreatic necrosis
3 Suppurative pancreatitis (abscess of the pancreas)

Inasmuch as there is no demonstrable necrosis in the first type and the lesion consists entirely of an interstitial edema it seems confusing as well as incorrect to classify it under the heading of acute pancreatic necrosis although in many instances probably it is followed rapidly by necrosis which may even involve the entire gland

According to the best surgical opinion the treatment of both acute pancreatic edema and acute pancreatic necrosis should be conservative and operation not performed if a definite diagnosis can be made

It is important to recognize the third type namely suppurative pancreatitis as in this operative treatment is indicated always as a life saving measure

Acute Pancreatic Edema

Frequently at operation in cases of cholelithiasis the head of the pancreas is found to be hard and swollen Formerly this condition was thought by surgeons to be chronic pancreatitis but it is now known to be due to edema Archibald as early as 1913 suggested that many case of acute epigastric pain lasting only a few hours were instances of mild pancreatitis He cited the case of a young man who had had severe

Roentgenological Diagnosis of Pancreatic Disease

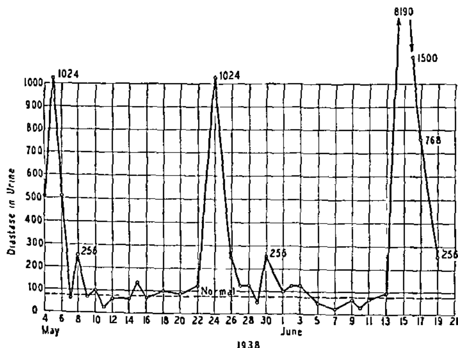
The only pancreatic disease in which a direct roentgenological diagnosis is possible is pancreatic lithiasis. Apart from this condition and the incrustation of the wall of a pancreatic cyst with calcium, x-ray diagnosis depends on indirect signs which are due chiefly to displacement of the neighboring organs by pressure of the enlarged pancreas. It is of greatest aid in the diagnosis of pancreatic cysts. According to their location the cysts are gastro-hepatic, retro-ventricular and gastro-colic. So-called bursa cysts produced by an encapsulated exudate in the bursa omentalis present a similar x-ray picture to that of gastro-hepatic cysts.

The enlargement of the head of the pancreas that occurs in acute pancreatic necrosis and in some cases of cancer of the pancreas is evident in the x-ray pictures by notching of the prepyloric part of the stomach and dilatation of the duodenum. Antiperistalsis of the dilated duodenum may be observed on fluoroscopic examination. Additional functional signs are delayed motility of the duodenum and meteorism, particularly of the transverse colon. Frostberg has described a characteristic form of the duodenum as the "inverted figure 3". This is produced by a dilatation of the duodenum in the region of the papilla biliaria. The medially directed angle is interpreted as due to a fixed adhesion. The distal part of the lesser curvature of the stomach can lie horizontally in consequence of the enlargement of the head of the pancreas.

Pancreatic Pain and Head's Zone

Katsch (1923) maintains that a pain in the epigastrium radiating to the left is characteristic of pancreatic disease. The right border of the painful area may be in the region of the gall bladder or in the middle line. The pain may extend along the costal border to the splenic or kidney regions or upwards in the left chest to the cardiac area or even to the left shoulder. Repeated attacks of pain radiating to the left in biliary disease associated with an increased diastase value in blood and urine probably are due to involvement of the pancreas as in a striking case recently reported by Loeffler (1938). In severe cases the pain may have the typical location at the onset but within a few hours may involve the entire upper abdomen. The French have regarded pain just above the umbilicus as characteristic of pancreatic disease. The pancreatic pain according to Katsch often is accompanied by a hyperesthetic area of the skin forming a half girdle extending from the epigastrium over the lower left ribs to the spines of the tenth to the twelfth thoracic vertebrae

two days to 64 The temperature was 37 7° C bilirubin 2 0 mgm per cent Rapid improvement followed On May 25 there was recurrence of pain in the upper abdomen and simultaneous increase of diastase to 1 0 4 Restoration to normal followed within a few hours After an additional period without symptoms and with normal diastase values he was seized again on June 13 with pain in the right upper abdomen again radiating to the left At the same time the diastase value rose to



Loeffler s case of recurrent acute pancreatic edema simulating biliary disease The marked rise in diastase value (Wohlgemuth s units) occurred in each of three attacks of epigastric pain See text

8 160 dropping in three days to 256 The leucocytes rose from 7 800 to 13 900 and the bilirubin in the blood to 1 4 mgm per cent

Cole (1938) reported a similar case with a chart like that printed above Associated with two attacks of epigastric pain there was a marked rise of diastase activity followed by a rapid fall within a day or two Gallstones were found in the stools following each of the two attacks Acute pancreatic edema was present at operation It was probably caused by transitory compression of the pancreatic duct by a gallstone

transient attacks of agonizing epigastric pain and tenderness Operation revealed a diffusely swollen pancreas without fat necroses or hemorrhage The patient recovered Zoepffel (1922) reported 4 similar cases in which at operation there was found an edema of the entire pancreas Sections of the pancreas were taken in 2 cases and on microscopic examination no evidence of necrosis was found All 4 recovered It is now recognized as the most common type of acute pancreatic disease Six proved cases were observed by Cole (1938) during a period of eighteen months

Acute pancreatic edema usually is found associated with disease of the biliary tract Out of 113 cases of biliary colic in Clairmont s clinic in which the urine was tested the diastase value was increased in 15 reaching 8 000 units or more in a number of instances It is regarded by some as an acute serous inflammation (Eppinger) and is held generally to be the initial stage of acute pancreatic necrosis Demel (1938) and Nordmann (1938) have seen what appeared at operation to be a harmless edema with slight symptoms progress to a total necrosis of the pancreas

Important studies on this disease have been made by Elman (1937) of Graham s clinic and by Cole (1938) of Chicago He as well as Zoepffel (1922) and Cole (1938) examined bits of tissue from the pancreas removed at operation and found no necrosis but Bircher (1929) found small areas of necrosis on the surface of the pancreas It is not a true inflammation and hence the term pancreatitis often applied to this disease is objectionable The edema may involve not only the head as is commonly stated but the entire gland (Archibald) The symptoms are the same as in the initial stage of acute pancreatic necrosis and in some cases are severe Without an elevation of the blood or urine diastase the clinical diagnosis rarely would be justified Knowledge of acute edema rests largely on the correlation of the symptoms laboratory tests and findings at operation

The report of an unusually instructive case of what was probably recurrent acute pancreatic edema has been published by Loeffler (1938) Chart I is a modification of one in his paper It shows in a striking manner the diagnostic value of diastase determinations of the urine made either every day or every other day as in this case over a period of nearly seven weeks During this time there were three attacks of acute pancreatic disturbance in a patient who presented the clinical picture of cholelithiasis but in whom no gallstones were found roentgenologically The patient a woman of 58 had pain in the gall bladder region occasionally after meals during the winter of 1937–38 On May 3 1938 sudden colicky pain occurred in the epigastrium radiating to the left There was diffuse tenderness of the entire abdomen but marked in the left epigastrium Diastase in the urine was 1 024 units on May 4 falling in

Etiology and Pathogenesis of Acute Pancreatic Necrosis

The association of disease of the biliary passages and acute pancreatic necrosis is undoubted. It occurs according to most statistics in 70 to 90 per cent of the cases. For many years following the publication of the famous case reported by Opie in 1901 the view was held that a frequent cause of acute pancreatic necrosis was the impaction of a gallstone in the ampulla of Vater. If the pancreatic duct opened into the ampulla above the stone a common channel would be formed by the biliary and pancreatic ducts with the result that infected bile might flow into the pancreatic duct, activate the trypsinogen and acute pancreatic necrosis result. In time it was realized that gallstones are found rarely in the ampulla in cases of acute pancreatic necrosis. They were present in only 1.4 per cent of 437 cases collected by Guleke and in only 4.5 per cent in Schmieden and Sebenings series of 1,278 cases. Even when a stone is present its size and the anatomical relations of the bile and pancreatic duct often are such that a common channel is not formed as has been shown repeatedly (Mann and Giordano, 1923).

Archibald (1919) suggested that in the absence of a gallstone the sphincter of Oddi, which is situated at the ampulla of Vater, might undergo spasm and thereby permit bile to flow into the pancreatic duct. In animal experiments Archibald found that irritation of the duodenal mucosa near the papilla induced a spasm of this sphincter to such a degree that it resisted pressure in the common duct three to five times greater than normal bile pressure. Fluids introduced into the gall bladder could be forced easily into the pancreatic ducts by increasing the pressure in the biliary passages. When the pressure in the biliary passages was varied from minute to minute the resistance of this sphincter was so marked that infected bile was driven into the pancreatic duct and produced fulminating pancreatic necrosis. In one cat in which the procedure of injection lasted twenty five minutes the animal died twenty minutes later with hemorrhagic necrosis of the entire pancreas. This theory, supported by these and other experiments, was accepted widely. In opposition to it Mann and Giordano claimed that the sphincter in man, when contracted, often closes both the bile and pancreatic ducts, thus preventing the entrance of bile into the latter. The work of Cameron and Nobel (1924), however, lent support to Archibald's theory. They impacted artificially a calculus in the ampulla of Vater at autopsy in a large series of human subjects. Then by forcing fluid down the common duct and noting whether it entered the pancreatic duct, they found a common and freely communicating system present in 66 out of 100 speci-

Acute Pancreatic Necrosis (Acute Pancreatitis)

The severe acute disease of the pancreas often called acute hemorrhagic pancreatitis is unlike that of any other organ because the disease is due to the destructive action of the pancreatic juice on the very tissue that formed it and the general symptoms that occur result from the absorption of toxic bodies produced by this autodigestion The term pancreatitis implies a bacterial origin and inflammatory nature of the disease which are false The erroneous conception that the disease is essentially an inflammation led to its surgical treatment which is now known to be not only ineffective but injurious

Opie and Meakins (1909) use the term acute hemorrhagic necrosis but acute pancreatic necrosis (Guleke 1912) or acute toxic necrosis of the pancreas seems preferable as the lesion is not always hemorrhagic The subdivisions made by Fitz (1889) into hemorrhagic and gangrenous forms of acute pancreatitis represent different stages in the same pathological process which begins with necrosis of the pancreas These forms cannot be differentiated by symptoms or physical signs From the clinical point of view it is well to group the different forms together under the name of acute toxic necrosis and to give up any attempt at subdividing them further

The fulminating form of the disease has been mistaken often for simple hemorrhage into the pancreas It was long held that hemorrhage into the pancreas apart from necrosis was a definite clinical entity and as a cause of sudden death it assumed considerable medicolegal importance The symptoms as given by Prince (1882) and others are those of fulminating toxic necrosis and it is probable that most if not all of the cases reported of simple hemorrhage were examples of this disease Opie and Meakins seem to have been the first to recognize the identity of the two conditions While it is possible that a sclerosed artery in the pancreas might rupture as it does in the brain and lead to pancreatic apoplexy without necrosis such an event must be excessively rare and certainly could not be an explanation of this type of hemorrhagic disease of the pancreas

Age and Sex — Acute toxic necrosis most frequently occurs between the ages of thirty and fifty It is about twice as frequent in males as in females Of 121 cases collected by Peiser (1902) 79 were in men 42 in women Of 44 cases observed by Koerte (1909) and his colleagues 30 were in males and 14 in females Gruber (1929) collected 94 cases that came to autopsy and of these 58 were in males and 36 in females These statistics bear out the statement just made as to sex incidence

Kaufmann (1927) in a series of 28 animals was not able in a single instance to produce pancreatic inflammation from infections of the gall bladder wall or of the glands draining it. Recent authoritative writers agree with Archibald that the theory is untenable.

Recent studies by Rich and Duff lead them to conclude that the usual cause of acute pancreatic necrosis is an obstruction in the branches of the pancreatic duct due to a metaplasia of the duct epithelium; dilatation of the portion of the duct and acini behind the obstruction results. These dilated acini would seem particularly liable to rupture during periods of increased pressure within the system such as occurs when the secretion of the gland is greatly increased as by a large meal or the ingestion of alcohol. The conclusions of Rich and Duff are supported by careful histological observations. Their view that obstruction of ducts within the pancreas rather than reflux of bile is the chief factor in the production of an acute pancreatic necrosis fail to explain, however, the close relation between biliary disease and acute pancreatic necrosis. The etiological rôle played by alcohol is undoubted; yet if this is due, as they think, to increased formation of pancreatic juice produced by this drug, it is surprising that in none of five patients recovering from acute pancreatic necrosis who were given the strongest known stimulus to secretion, namely the intravenous injection of pure secretin, did a recurrence of the disease take place (Agren, Lagerlof and Berglund, 1936).

Trauma of the pancreas may lead to its necrosis, but only when the pancreatic juice has been activated. If after crushing the gland the main blood vessels are tied, acute pancreatic necrosis develop, and about half of the animals die (Levin, 1907). Injuries, inflammations or thrombosis affecting the pancreas lead to autolysis of some of the pancreatic cells. Autolyzed pancreas is toxic. If the sterile pancreas of one dog is placed in the peritoneal cavity of another dog, as the gland autolyzes symptoms of poisoning rapidly develop similar to those seen in acute pancreatic necrosis in man. We found that a portion of the pancreas of a newly born puppy placed in the subperitoneal connective tissue of the anterior abdominal wall of another dog caused the death of the animal within forty-eight hours, while larger pieces of pancreas from adult dogs placed in the spleen caused no observable ill effects. These results confirm Fischler's findings that the liver has a detoxicating influence on the products of pancreatic autolysis. The poisoning formerly was thought to be due to trypsin, but probably it is the result of the absorption of split products of protein resulting from the intra vitam digestion of the pancreas (Petersen, Jobling and Eggstein, 1916). Goodpasture and Clark (1919) found a toxic constituent present in the fresh gland, either a

mens If the presence of bile in the pancreatic duct was the common cause of acute pancreatic necrosis one would expect to find at autopsy that its lining would be stained with bile in cases of acute pancreatic necrosis but such rarely is the case It is a routine autopsy procedure to compress the gall bladder with considerable force to test the patency of the cystic and common ducts By clamping the tip of the papilla biliaria and then exerting pressure on the gall bladder bile is forced readily into the pancreatic duct when bile duct and pancreatic duct open together in the ampulla (Rich and Duff 1936) Staining of the pancreatic duct in Opie s case referred to above is thus explained as the protocol states that by very firm pressure on the gall bladder several drops of bile can be squeezed with difficulty into the duodenum

Additional evidence against the view that entrance of bile into the pancreatic duct is a frequent cause of acute pancreatic necrosis is furnished by (1) the recent discovery of Harms (1927) that during the height of digestion which is the time acute pancreatic necrosis usually develops the pressure in the pancreatic duct is higher than in the common bile duct (2) pancreatic ferments have been found by Popper (1933) in the extirpated gall bladder in 20 per cent of the cases of acute pancreatic necrosis examined This observation indicates that the pancreatic juice may enter the biliary system and there become activated by the bile It is supported by the work of Welfer (1939) who showed that india ink introduced into the terminal end of the common duct of the dog was recovered later in the gall bladder He showed further that the pancreatic juice may be activated in the biliary tract and that pancreatic juice introduced into the gall bladder produces pathological changes in its wall If it were reinjected later into the pancreatic duct it might set up acute necrosis of the gland but this would not occur as Rich and Duff have shown unless the duct acinar system is ruptured

Acute pancreatic necrosis can be produced experimentally without the injection of any material into the pancreatic duct Years ago Hess (1909) demonstrated this by tying the ducts at the height of digestion after a full meal My associates and I have produced acute pancreatic necrosis repeatedly by this procedure even in fasting animals The experiment demonstrates that the trypsinogen is activated readily within the pancreas without the addition of bile or bacteria to the pancreatic juice

The belief that acute pancreatic necrosis was caused by a spread of infection from an inflamed gall bladder to the pancreas by way of the lymphatics was supported strongly by Arnsberger (1911) in Germany and Deaver (1914) in this country and gained wide acceptance Archibald points out clearly its lack of anatomical support and his associate

afterwards for any other lesion As they occur only in cases of pancreatic disease their presence on opening the abdomen frequently reveals to the surgeon the existence of unsuspected pancreatic necrosis

The gangrenous stage of pancreatic necrosis has been described admirably by R H Fitz The gland in the early stage is swollen dark red and soft or it may be transformed into a dark slate colored mass At the end of about ten days the pancreas is often dark brown dry and firm Throughout its substance areas of hemorrhage alternate with yellow spots of softening At the end of the second week the organ may form a soft black mass while the lesser omental cavity contains a large quantity of chocolate colored fluid containing bluish black clots

Symptoms of Acute Pancreatic Necrosis

The patients usually are of middle age and obese Frequently there is a history of over eating and alcoholism *Often there have been previous* attacks similar to the present but less severe or the patient has had repeated attacks of epigastric pain It is now known that mild attacks of pancreatic necrosis are not rare and many of the seizures attributed to gallstones are really due to preceding attacks of pancreatic necrosis from which the patient has made speedy recovery

The attack begins with intense pain in the upper abdomen unequalled in the worst cases by that in any other acute abdominal condition (Archibald) The onset usually is sudden The history often is obtained that the patient was seized with agonizing pain a few hours after eating a heavy meal The pain usually is mistaken for gallstone colic The *severity of the pain is the most striking feature in the early stage of the* disease It is most marked in the epigastrium or just above the umbilicus Sometimes it is felt only to the left of the median line but it may occupy the gall bladder region alone Pain in the epigastrium radiating to the left of the mid line is characteristic of the milder attacks It may radiate around the abdomen to the back girdle fashion or to the left shoulder or it may extend down into the lower abdomen Vomiting quickly follows the onset of the pain The act is repeated again and again with short intervals and without bringing relief The vomitus often contains bile The upper abdomen is slightly swollen In the early stages there is no evidence of peritoneal involvement The abdomen often can be deeply palpated and although the resistance is increased rigidity of the muscles is rare A resistance may be made out sometimes on deep palpation extending transversely across the abdomen Tenderness extending to the left from the gall bladder region is highly suggestive

protein or in combination with a protein The reactionary peritoneal exudate in acute pancreatic necrosis is non toxic and has a protective value (Whipple and Goodpasture 1913)

It has been shown clinically that rapidly fatal necrosis of the pancreas may follow an injury to the pancreas such as has resulted from the kick of a horse or the passage of a wheel of a wagon over the abdomen Beneke (1911) believes that a sudden reflex ischemia of the pancreas may lead to acute necrosis He often found erosions of the stomach and areas of tissue necrosis in the pancreas at autopsy three or four days after an operation in the region of the gall bladder Possibly more important than mechanical factors are functional disturbances of the nervous mechanism controlling the circulation in the gland As a result of impaired blood supply the nutrition of the cells of the pancreas is injured and thereby abnormal split protein products are produced and trypsinogen is activated Thus circulatory disturbances and fermentative processes acting together may inaugurate the autodigestion of the gland

After the trypsin has attacked the tissues the lipase of the pancreatic juice is able to act on the fat cells producing the typical whitish opaque areas of fat necrosis The scattered nodules of fat necrosis in different parts of the peritoneal cavity are not caused by a diffusion of the pancreatic juice as these areas of fat necrosis are covered with well preserved endothelial cells They are due to the passage through the lymph and blood channels of activated pancreatic secretion which by means of its lipase steapsin converts the neutral fat into fatty acids and glycerol

Pathological Anatomy of Acute Pancreatic Necrosis

The pancreas in the severe forms of acute toxic necrosis with hemorrhage is found at autopsy to be enlarged either uniformly or at one end usually the head It is often friable and of diminished consistence The surface is a varying shade of red and on section the color depending on the extent of the hemorrhage may be dark red reddish brown violet or even black It may have a uniform dark color or present a mottled appearance There may be bands and spots of translucent yellow which are formed of fat tissue and opaque white specks and streaks due to fat necrosis These areas of fat necrosis although most common in and about the pancreas are found often in the fat tissue at a distance usually in the mesentery omentum and parietal peritoneum They have even been present in the subcutaneous fat and the pericardium In size they vary from a pin point to a pea Their appearance is so striking and distinctive that once seen and recognized they cannot be mistaken easily

severity and persistent in spite of morphine Its onset is sudden often after a heavy meal at the height of digestion The location is in the epigastrium especially to the left of the gall bladder region but in severe cases may involve the entire abdomen (2) There is almost always *vomiting* often abundant occasionally bloody with no lessening of the pain (3) Severe *collapse* (4) The temperature may be subnormal normal or elevated (5) No muscle spasm *Acute pancreatic necrosis develops behind a soft abdomen* (6) Tenderness in epigastrium to the left of the gall bladder (7) Rapid pulse (8) Oliguria (9) *Often subicterus* (10) Laboratory aids to diagnosis leucocytosis hyperglycemia increased bilirubin in blood (quantitative van den Bergh) and especially elevated diastase values in blood and urine (11) By x ray the duodenal ring may be widened the bulbus duodeni compressed barium accumulates in the duodenum as a result of hypotonia

Differential Diagnosis — In the large series of cases over 2 000 in number collected by Schmieden and Sebening (1927) from German clinics a correct preoperative diagnosis was made in only 21 8 per cent The most frequent erroneous diagnoses in a series of 118 cases analyzed by Brocq were perforated ulcer 25 times ileus 23 peritonitis 15 appendicitis 13 cholecystitis 11 times Against perforation peritonitis is the absence of muscle spasm and the coexistence of severe shock and a relatively good pulse which in perforative peritonitis usually becomes accelerated more quickly than in acute pancreatic necrosis Against ileus is the fact that the gastrointestinal tract is not completely obstructed and there is no fecal vomiting Against obstruction of the small intestine is the absence of widespread tympany the existence from the onset of epigastric pain furthermore the rarity with which occlusion of the small intestine is located in the epigastric region In distinguishing between peritonitis due to perforating ulcer and acute pancreatic necrosis it is important to remember that in the latter condition the local tenderness is slight in comparison with the severity of the abdominal pain Agonizing continuous pain in the upper abdomen unrelieved by morphine points strongly to acute pancreatic necrosis The board like hardness of the muscles is absent the abdomen is somewhat distended tense but often one can palpate quite deeply The diagnosis often becomes clearer after the first day In acute pancreatic necrosis the signs and symptoms remain localized chiefly in the epigastrium while in perforated ulcer the evidence of peritonitis in the lower abdomen becomes marked (Archibald) In perforated ulcer x ray most probably would show air free in the abdominal cavity especially up under the diaphragm It is most important to consider the possibility of acute pancreatic nec

of acute pancreatic necrosis (D F Jones 1936) Great care should be taken to determine accurately the degree and the distance to the left of the area of tenderness

When first seen the patient appears very sick The skin is pale and moist The pulse is rapid while the temperature often is normal or sub normal There is a striking disparity between the scanty signs of ab dominal disease on examination and the evident seriousness of the patient s condition

The bursa omentalis frequently becomes distended with a bloody exudate When this fluid contains debris formed from necrotic pan creatic tissue sometimes it is mistaken at operation for thin bloody pus Distention of the lesser peritoneal sac often gives rise to a large tumor mass usually felt in the left flank In severe cases death usually occurs between the second and fourth day There is frequently a great in crease in the leucocyte count which often reaches between 20 000 to 40 000 per cu mm and may rise to 50 000 Toxic changes in the leu cocytes occur consisting of many vacuoles and basophilic rods (Schieren) The granules are only slightly enlarged A marked leucocytosis in this disease is prognostically unfavorable (Nordmann)

Diagnosis of Acute Pancreatic Necrosis

Although the diagnosis rarely can be made with certainty without the aid of the diastase test of the blood or urine a probable diagnosis is possible on clinical examination in typical cases of acute pancreatic necrosis The preceding lighter attacks the history of gallstone colic obesity and alcoholism the sudden onset with severe shock the stormy course the localization of the pain in the epigastrium especially to the left of the median line where meteorism soon develops and where there appears on deep palpation an indefinite resistance with tenderness but without muscle spasm the contrast between the condition of collapse and the fairly good pulse these features taken together give a fairly typical clinical picture

Tenderness should be elicited by careful finger point palpation Archibald emphasizes the importance of an area of epigastric tenderness in diagnosis It rarely extends more than 2 5 cm to the right of the median line and usually an equal distance to the left The maximum tenderness usually is in the median line In the subsiding stage there is often tenderness in the left costoiliac space behind

As an aid to diagnosis the following points are helpful (1) *Pain* is the dominating symptom in the clinical picture It is often of agonizing

Among other American observers to report improved results from conservative treatment are Trasoff and Scarf Three of their 4 patients subjected to early operation died whereas of 12 not operated upon, 9 recovered

When those surgeons who have adopted the conservative treatment discover at operation that there is an acute pancreatic necrosis they leave the pancreas alone Nordmann (1938) and Demel (1938) both state they have not even drained off the bloody peritoneal exudate and yet patients have recovered and the free fluid soon was absorbed The surgical procedures have been based as Nordmann (1938) has pointed out clearly on a wrong conception of the disease namely that it is an infection and the use of the term pancreatitis has aided in keeping alive this error In acute pancreatic necrosis there is an auto intoxication and autodigestion and the disease tissue is free from bacteria The symptoms are due to the absorption of toxic products from the necrotic gland by the blood vessels of the pancreas Attempts to remove the products of necrosis by drains or cutting the capsule of the gland as was formerly advocated do not lessen this absorption of poisons by the pancreas The peritoneal exudate is non toxic the fat necroses are harmless and the necrotic tissue if the patient recovers is replaced by connective tissue The patient poisoned by the absorption of split proteins is more or less in collapse and due to his condition even slight operative procedures often prove fatal

Outline of Treatment Advised — Intravenous administration by the drop method of 5 per cent glucose with insulin is recommended to make up the body water lost by vomiting If there is little or no loss of water solutions containing a higher percentage of glucose are of value Bernhard holds that the pancreas should be maintained in a resting state by withholding fluid by mouth and administering atropine V Bergmann (1938) believes that an absolute fast should be maintained for three or four days and no water or other fluid given as even water can cause a secretion of hydrochloric acid After the fast he gives a carbohydrate diet that is fat free and as low in protein as possible for a longer period Such a rigid regime is based on theoretical grounds only No one has reported better results than Puhl of Kiel and he gives 200 c c of a hot 15 per cent magnesium sulphate solution several days in succession with the object of increasing the flow of secretion and lessening existing complications due to gallstones He has treated 26 cases with only one fatality (3 9 per cent)

The conservative treatment employed on the Harvard Surgical Service at the Boston City Hospital as described by Lium (1938) consists of

iosis in the presence of any acute upper abdominal condition In tho e clinics in which the use of the diastase test has been employed in cases of *acute pain in the upper abdomen the percentage of correct diagnoses* has been increased greatly

It may be difficult to distinguish between the acute type of mesenteric thrombosis and acute pancreatic necrosis but in the former, severe shock is rare and the passage of blood may settle the diagnosis

Agonizing pain in the upper abdomen not relieved by morphine always should bring this relatively rare disease to the physician s mind provided coronary thrombosis angina pectoris and food poisoning reasonably can be excluded In such cases the diastase value of the urine should be determined at once

Treatment of Acute Pancreatic Necrosis

In an attempt to reduce the high mortality early operation was advo cated and extensively employed but without success as the death rate remained unaltered ranging between 50 and 60 per cent In 1929 Polya Walzel and Nordmann opposed the early operation and advised after convalescence was well established the so called interval operation on the gall bladder for latent biliary disease Since then the conservative treat ment has had more and more adherents as the favorable results which were obtained when no operation is attempted became known For example De mel in Vienna from 1926 to June 30 1934 had 23 cases An operation was performed on all but one of these The mortality was 78 3 per cent From July 1 1934 to December 31 1937 he had 45 cases Four were operated in the early stage owing to a false diagnosis with three deaths Em ploying conservative treatment on the remainder the death rate fell to 24 4 per cent A group of leading surgeons in Europe do not now operate on any case of acute pancreatic necrosis in which a definite diagnosis is made Nordmann took this *position at the German* Congress of Surgeons in 1938 In the discussion that followed the reading of his paper no one opposed this view The statistics speak eloquently in its support In Nordmann s own clinic the death rate has fallen from 50 to 24 per cent Walzel reports a drop from 86 per cent to 28 per cent and Haberer from 53 6 per cent to 23 1 per cent In 1935 Henderson and King analyzed the results on 60 cases of acute pancreatic necrosis treated at the Boston City Hospital The mortality was 53 per cent In a recent report from *the same hospital Lium (1938) states that this has been reduced* by con servative measures to 25 per cent The only patients who died in his small series were those who were operated upon early three out of four

leucocytosis with many band forms of cells are of diagnostic value In such a case an area of tenderness may develop above the umbilicus in the left lumbar region or in the subphrenic space These are signs pointing to the location of a secondary abscess formation

It is of the utmost importance to recognize an abscess of the pan creas as incision and drainage are in most cases life saving The treat ment of suppurative pancreatitis always is surgical

PANCREATIC CYSTS

The cysts of the pancreas form an interesting group of abdominal tumors They are so rare that among 6 708 autopsies only 3 pancreatic cysts were found (Hale White 1900)

Pathologically they can be arranged in three groups (1) cystic neoplasms cystadenoma papilliferous cystoma (2) retention cysts (3) pseudocysts The last class is the largest and most important clini cally Cysts may occupy the tail of the pancreas rarely the head but most pseudocysts are produced by the collection of blood or the products of pancreatic secretion and digestion in the lesser peritoneal sac The foramen of Winslow becomes closed and after recovery from the acute stage of pancreatic necrosis a pseudocyst may develop The blood may be absorbed leaving a clear fluid or hemorrhage may take place into a formed cyst They have no true wall and no epithelial lining to the inflammatory tissue that bounds the cavity The relation of the cysts to pancreatic necrosis is clear In nearly half of the cases the symptoms followed an attack which was fairly characteristic of acute pancreatic necrosis Nearly 30 per cent of the cases resulted from trauma usually blows on the abdomen Injury to the pancreas produces pancreatic necrosis as a result of which blood or products of digestion accumulate in the lesser peritoneal cavity forming a cyst Often at operation the relation of the pseudocyst to the pancreas and the true nature of the cyst are not discovered What one surgeon calls a hematoma or effusion into the bursa omentalis another calls a pseudocyst

Symptoms of Cysts

Pain is the chief symptom but it varies so in location intensity and character that it is of slight diagnostic value It often is present for months or even years before the tumor is palpable They are the most painful of all abdominal cysts (Chauffard 1915) A marked and pro gressive loss of weight is a striking feature in many cases

parenteral fluids, gastric lavage and sedation largely in the form of barbiturates A nasal tube is left in place for ready aspiration and gavage Three times a day 12 c c of 50 per cent magnesium sulphate are introduced into the nasal tube in order to facilitate drainage of bile into the duodenum The fact that all eight patients in Lium s series who received this treatment recovered at least would indicate that the introduction of some fluid into the duodenum during the course of acute pancreatic necrosis is not attended with any serious danger

Combating the pain is of great importance Hot compresses are of value Morphine is said to contract the sphincter of Oddi and for this reason it is well to use it sparingly Repeated injections of papaverine hydrochloride are recommended and only when they fail to relieve the pain should morphine be given

Suppurative Pancreatitis (Abscess of the Pancreas)

Two forms of suppuration of the pancreas exist The first and more important is the suppuration that may follow acute toxic necrosis due to the growth of the pyogenic bacteria in the necrotic tissue This is the suppurative pancreatitis described by Fitz (1889) It may result also from the extension of an inflammatory process in neighboring organs most commonly a peptic ulcer in stomach duodenum or jejunum In the second form the pancreas is the seat of metastatic abscesses Clinically this type has little importance among diseases of the pancreas as it is simply a local manifestation of general blood infection In both varieties the abscesses may be single or multiple Areas of softening in the necrotic tissue in acute pancreatic necrosis often are mistaken for true abscesses at operation but microscopic examination of the material shows few pus cells and cultures are sterile While usually only a portion of the pancreas may be involved in suppurative pancreatitis in some instances the whole gland may lie as a sequestrum in a pus cavity which usually occupies the lesser peritoneal sac The gland may contain abscess cavities of various size The organ is enlarged and indurated Suppurative pancreatitis is the rarest type of acute pancreatic disease Among 20 cases of acute pancreatic necrosis seen at the Massachusetts General Hospital and in private practice analyzed by Balch and Smith (1910) 16 were hemorrhagic 3 gangrenous and only 1 suppurative The disease resembles suppurative inflammation of other organs It rarely runs an acute course Symptoms may persist for weeks High fever and chills in acute pancreatic necrosis point to suppurative pancreatitis but on the other hand it may develop insidiously A return of fever and a

more easily felt by pushing them forward but the distended stomach will press backward and may cover the pancreatic cyst Mesenteric cysts occupy the umbilical region and can be moved easily in all directions

The x ray examination has proved of great value in diagnosis This has been dealt with already in the discussion of roentgenological diagnosis of pancreatic disease

The previous history is important in diagnosis In the majority of cases a severe trauma or an attack of unrecognized acute pancreatic necrosis preceded the development of the tumor

Treatment of Cysts

Cysts have been treated by puncture by incision and drainage and by extirpation Exploratory puncture is both dangerous and ineffectual The operation to be employed in most cases is incision with marsupialization This procedure generally is successful in effecting a cure of pseudocysts although the resulting fistula may discharge for a long time The first complete extirpation of a pancreatic cyst was done by the American surgeon Bozemann in 1881 A diet rich in fat and protein as suggested by Wohlgemuth may diminish the secretion of pancreatic juice and has aided the healing of fistulas in some cases but has failed in others

Adenomas of the Pancreas (Hyperinsulinism)

The first paper on adenomas originating in the islands of Langerhans was by Wilder Allan Power and Robertson (1927) They described a case of malignant adenoma with metastases in the liver The cancer cell were morphologically identical with the cells of the islands and from the tumor masses insulin was extracted In later cases there were island adenomas without metastases Clinically in these cases there are increasing manifestations of hypoglycemia with attacks of insulin shock The condition may progress to a comatose state If in spite of a high carbohydrate diet the blood sugar remains low and the seizures continue an exploratory operation is indicated Whipple (1935) has operated on seven cases of hyperinsulinism and excised one or more adenomas of islet tissue in each In one case four fifths of the pancreas was excised All his cases were cured but occasionally mild diabetes has developed after the operation Whipple and Frantz have reviewed all the cases of hyperinsulinism reported up to 1936 In diabetes a regeneration of the island apparatus can occur leading to adenoma formation with resulting

Pressure symptoms of different forms have been observed. Ascites may result from pressure on the portal vein and edema of the legs from compression of the vena cava. On abdominal examination an elastic swelling is discovered in the epigastrium. As it increases in size it moves forward and can be felt directly under the anterior abdominal wall. It may appear high in the epigastrium above the lesser curvature of the stomach or so low as to have the transverse colon above it.

The *etiology* of most cysts has not been discovered. In a total of 128 cases collected by Schmieden 28 were due to acute pancreatic necrosis, 16 to trauma, 11 to tumor and in 73 the cause was not known.

Evidence of obstruction of the pancreatic ducts such as fatty diarrhea, relatively common in cancer, is very rare in the case of cysts because the latter almost never involve the head of the gland. As the changes in the pancreas rarely are serious glycosuria is not common. It occurred 9 times in 134 cases (Oser 1898). The cysts sometimes develop very slowly. These usually are true cysts. Hulke (1892) saw one that had existed forty years. The pseudocysts may develop quickly after trauma or an attack of acute pancreatic necrosis. They may disappear suddenly due to discharge of the cyst into the intestine at times with resulting diarrhea. In Payr's (1898) case the tumor disappeared and recurred three times in two months.

Diagnosis of Cysts

A fluctuating tumor in the epigastrium, especially if situated to the left of the median line, always is suggestive of pancreatic cyst. The physical signs are essential to diagnosis and the most important of these are the fluctuating feel of the tumor and its relation to the stomach, liver and colon. They rarely move with respiration but to this there are exceptions, and although usually fixed in position some cysts can be moved freely from side to side. In size the cysts usually vary from that of a small apple to that of a man's head. Occasionally cysts are so large that they fill the abdomen. The patient should be examined in the erect as well as in the recumbent posture, as the sagging of the cyst may separate it from the liver by a tympanitic zone. It is important to remember that pancreatic cysts are retroperitoneal and hence often partially covered by stomach or transverse colon. Inflation of stomach and large intestine with air is of aid in diagnosis. The distended colon will lie below or partially cover the cyst. An echinococcus cyst of the liver, a dilated gall bladder or a cyst of the spleen may be confused with a pancreatic cyst. Filling the stomach with air makes these other tumors

Compression of the duct with resulting jaundice usually results early when a cancer is growing in the head of the gland Pressure on other tructure leads to great variations in the clinical picture The duodenum may be compressed leading to gastric stasis and dilatation Pressure on the portal vein gives rise to ascites and the growing mass may press on the inferior vena cava causing edema of the legs Extension of the growth usually is through the lymphatics and the cancerou lymph nodes may form large masses in front of the vertebrae Metastases generally are present in the liver but they do not form large tumors and rarely project above the surface of the liver

Symptoms of Carcinoma of the Pancreas

Digestive disturbances are pre ent nearly always but they are not distinctive They consist of loss of appetite acid eructations epigastric discomfort nausea and vomiting HCl in the gastric juice may be present or absent The bowels often are constipated

Pain is a common symptom occurring in over half of the cases Usually it is severe and often is located deep in the epigastrium and may radiate to the back It may resemble the gastric crises of tabes When severe it is thought by Chauffard (1908) to indicate that the tumor involve the body of the gland There is some evidence for the view held by many writers that the severe epigastric pain is due to pressure of the neoplasm on the solar plexus Intermittent colicky pain is ascribed in some cases to obstruction of the flow of pancreatic juice through the ducts but probably is due more often to biliary colic Epigastric tenderness usually is associated with the pain

Jaundice is the mo t striking symptom It is present in about 75 per cent of the ca e It may come on gradually or the onset may be sudden It is p rmanent and progressive and leads to intense icterus The association of deep jaundice with a large gall bladder is characteristic of cancer of the pancreas It illustrates Courvoisier s law that biliary obstruction due to the pressure of a tumor is accompanied by an enlarged gall bladder whereas in gallstone obstruction of the common duct the gall bladder is shrunken Ecklin (1896) found the gall bladder dilated in 121 out of the 139 instance of obstruction not due to stones Although the gall bladder is found dilated at operation and at autopsy it does not follow that it can always be felt through the abdominal wall Death usually occurs within a few months and sometimes within a few weeks after the onset of jaundice The average duration of life after thi symptom appears is four months

spontaneous hypoglycaemia (Terbruggen, 1933) This is discussed also in Vol IV Chapter V-B

Carcinoma of the Pancreas

Cancer of the pancreas has been regarded as the most common disease of this gland It is certainly the one recognized most often during life and the one found most often at autopsy but in the light of present knowledge there can be little doubt that acute pancreatic edema occurring in mild attacks is of more frequent occurrence Sarcoma may involve the pancreas Kakels in 1902 collected 21 instances of which at least 10 were primary Clinically sarcoma cannot be distinguished from cancer In tuberculosis of the pancreas tumor like caseous masses have been described but tuberculosis of this gland has no clinical importance Gummata are rare but they occur and may be mistaken for true tumors Benign tumors are very rare

Incidence and Pathological Anatomy of Carcinoma of the Pancreas

About 2 per cent of the deaths from cancer are due to involvement of this organ It is much more common in men than women Secondary involvement is somewhat more frequent than primary growth and is due usually to direct extension from a neighboring organ as the stomach duodenum or bile ducts Metastases in the pancreas are rare

In primary cancer the head of the gland is involved in about two thirds of the cases In Kiefer s (1927) series of 192 cases the head was involved chiefly in 119 the body in 15 the tail in 16 and in 72 the growth involved more or less of the entire gland

Usually the tumor is an adenocarcinoma and develops from the ducts or acini The islands of Langerhans generally are left intact by the tumor as it extends through the gland while the acini are atrophied or destroyed The growth rarely forms a tumor larger than a goose egg It is usually firm and hard In many instances the cancer is spread diffusely through the pancreas and its place of origin cannot be made out In this type the gland although usually enlarged may be atrophied To distinguish this latter form of diffuse cancer from chronic interstitial pancreatitis may require a careful histological examination

Pressure of the growth leads to obstruction of the ducts within the pancreas and this is always followed by atrophy and sclerosis of the portion of the gland from which the duct arises In more than 50 per cent of subjects the common bile duct is surrounded by pancreatic tissue

amination is of frequent occurrence (Dorner 1916) HCl was absent in the stomach contents in 5 out of 10 cases of cancer of the pancreas examined by Heiberg (1911) An absent or diminished gastric secretion may aid in diagnosis as in uncomplicated obstruction of the common bile duct usually there is hyperchlorhydria Glycosuria occurs in from 10 to 25 per cent of the cases but often it is intermittent and rarely is severe Ascites due to pressure on the portal vein occurs in about half the cases

Diagnosis of Carcinoma of the Pancreas

Jaundice increasing in intensity with a palpable gall bladder is a characteristic syndrome in cancer of the pancreas The liver usually is not enlarged A tumor may be felt in the region of the pancreas but this is rarely of help in diagnosis In obstructive jaundice from stone the jaundice may be intermittent the gall bladder is small and often there is an increase of temperature In cancer of the pancreas the temperature is normal or subnormal

The cases without jaundice are very difficult to recognize yet they form 10 to 25 per cent of the cases of cancer of the pancreas that come to autopsy They take their origin usually in the body of the gland and may extend diffusely through the organ Severe epigastric pain is common in this type of cancer

In some cases no local symptoms attract attention I once made an *autopsy on an old* man whose only complaint had been increasing weakness So suspicious were some of his friends of poisoning by his attendant that his body was disinterred about six months after death in order to determine the cause of death A cancer of the pancreas was found with metastases in the liver

The x ray may prove to be a valuable aid in diagnosis Enlargement of the head of the pancreas especially downward by traction on the mesenteric attachment produces a kink in the duodenum with characteristic signs of stenosis of the duodenum on fluoroscopic examination After a bismuth meal the duodenum may appear entirely and continuously filled

The difficulty of diagnosis that exists in many cases should be emphasized During the past four years in my clinic we have failed to make the diagnosis *in at least 5 cases None of these were* jaundiced and none had bulky light colored stools Glycosuria was not present X ray studies of the gastrointestinal tract were negative One patient had indefinite abdominal pain the others did not All had a striking

The temperature remains normal or subnormal Loss of weight is progressive and cachexia develops In every one of the twelve cases studied in our Diagnostic Hospital during the past five years the weight loss has been marked It was the most constant symptom in this series of cases and in that of Ransom (1938), occurring in 95 per cent of his cases and averaging 30 pounds

A tumor in the epigastrium is felt in only a small proportion of the cases DaCosta found its presence recorded in only 13 out of 137 cases Mirallie (1893) in about 30 per cent It is sometimes so small that it may be overlooked easily at operation Even when a tumor has attained a considerable size it may be difficult to distinguish it from the surrounding tissues by palpation It is deeply seated and usually there is marked pulsation transmitted from the aorta A tumor may be of very small size even when through its growth it has led to a patient s death

Signs of obstruction of the pancreatic ducts should be sought for carefully in all cases of suspected carcinoma Mirallie (1893) found only 9 cases with fatty stools among 113 instances of cancer of the pancreas Fitz was able to find only 13 cases recorded in the literature up to 1903 There can be little doubt that the reason fatty stools are found so rarely is because systematic examination of the feces is neglected I analyzed the feces in 7 cases of cancer of the pancreas and in 6 of the 7 there was 50 per cent or more of fat in the dried feces One small clay colored stool that did not look fatty was found to contain 53 per cent of fat Tileston (1911) examined the stools in 5 cases of cancer of the pancreas and found that the per cent of fat ranged from 51 to 69 and that 46 to 76 per cent of the fat taken in the food was lost in the feces Tileston and I both worked at the Massachusetts General Hospital and together found in that institution and in private practice within a period of a few years 11 cases of cancer of the pancreas with fatty stools which were only two less than all the reported cases in the literature up to 1903

Obstructive jaundice without pancreatic disease it should be remembered leads to clay colored fatty stools but the stools usually are formed and rarely are bulky Free fat or oil never is seen There are very few muscle fibers to be seen Absorption studies show that the fat loss in the feces in occlusion of the common duct is seldom more than 40 to 45 per cent of the intake The characteristics of the stools in obstruction of the pancreatic ducts have been described in the earlier part of this chapter

Compression of the duodenum by the growing tissue may lead to an increase of the gastric symptoms as a result of stasis Slight stenosis of the lower end of the duodenum demonstrable in roentgenological ex

not encouraging The more human standpoint as Archibald says lies in palliation rather than radical removal Nature after all must be allowed some rights Our old friend with the scythe provided he come without pain and quietly lays his hand perhaps more gently upon the patient than does the surgeon

Chronic Pancreatitis

Much confusion exists regarding the cause the frequency the pathology and the diagnosis of chronic pancreatitis This is largely due to the fact as Osler has pointed out that the personal equation on the part of surgeons and laboratory workers has been such an important factor in the studies that have been made

Pathology of Chronic Pancreatitis

There are two forms of chronic pancreatitis (1) *Chronic interlobular pancreatitis* is characterized by an overgrowth of connective tissue between the lobules Wide bands of fibrous tissue may form This follows obstruction of the ducts or infection ascending the ducts Large gall stones in the diverticulum of Vater sometimes lead to this form of pancreatitis (Opie 1907) If the ducts are occluded atrophy of the gland with an overgrowth of connective tissue results The islands of Langerhans are not destroyed even in advanced interlobular sclerosis Diabetes rarely is associated with this form of pancreatitis (2) *Chronic interacinar pancreatitis* is produced by atrophy of the acini and a growth of connective tissue between the acini with slight involvement of the interlobular septa The islands of Langerhans often are degenerated or sclerosed Some cases seem due to obliterating endarteritis (Hoppe Seyler 1904) In the rare disease hemochromatosis this form of pancreatic sclerosis occurs

Much attention has been paid by surgeons to a localized swelling of the head of the pancreas associated with jaundice which has been regarded as a form of chronic pancreatitis Riedel in 1896 first called attention to this pathological condition In a case of intense jaundice which had lasted several weeks he found a tumor of stony hardness in the head of the pancreas the size of a small apple which he felt was undoubtedly a carcinoma The gall bladder was drained and the patient recovered He concluded that the swelling was due to chronic pancreatitis In the light of present knowledge probably it would be regarded as acute interstitial pancreatitis

loss of weight ranging from fifteen to forty one pounds In three the sedimentation rate was increased in one instance it was 87 mm in one hour (Westergren) Stern (1938) reported two cases in which the diagnosis verified at autopsy was made on a disturbance in carbohydrate metabolism and an increased sedimentation rate in the absence of characteristic symptoms

Treatment of Carcinoma of the Pancreas

If steatorrhea and creatorrhea exist dietary measures are clearly indicated Better absorption can be obtained sometimes by the use of fresh pancreas or pancreatic ferments but my experience has been disappointing Although absorption studies showed slight increase in absorption as described in earlier pages the patient continued to have frequent bulky stools and the general condition did not improve If jaundice exists attended by severe pruritus which cannot be relieved by local applications the advisability of cholecystgastrostomy or cholecystduodenostomy should be considered

One of my patients died from cholemia with hemorrhagic diathesis Her life possibly could have been prolonged many months by anastomosis of the gall bladder with the stomach or duodenum as the autopsy revealed a very small cancer in the head of the pancreas and no metastases The average duration of life after a cholecystenterostomy is six to eight months One of Archibald s lived three years in comfort and was able to work The distressing itching at night due to icterus was controlled in one of my patients by a dose of 7 mgm of morphine combined with 0 2 mgm of scopolamine subcutaneously The dose did not have to be increased during a period of three months Partial pancreatectomy for malignant disease has been attempted with an operative mortality of 50 per cent It is claimed that total excision of the pancreas for cancer has been performed three times (Billroth Tricomi Franke) As diabetes did not ensue it is evident that some pancreatic tissue was left All three died of recurrence Whipple (1935) and associates after a preliminary cholecystgastrostomy and a gastroenterostomy removed the second and third portions of the duodenum with the head of the pancreas in 5 cases One of these patients was well two years after the operation In a later paper (1938) Whipple stated that there were defects in the operative procedure and death resulted from choleangitis and hepatitis He now proposes to anastomose the gall bladder to the jejunum instead of to the stomach

It is evident that the operative treatment of cancer of the pancreas is

Etiology of Chronic Pancreatitis

In a series of 30 cases of chronic pancreatitis studied by Opie 17 were in males and 13 in females Over 80 per cent of the cases occurred after the fortieth year The most frequent cause of the disease is partial or complete occlusion of the main pancreatic duct This is due usually to cancer and much more rarely to pancreatic calculi and to large gall stones in the diverticulum of Vater compressing the pancreatic duct Permanent occlusion of the pancreatic ducts by ligation causes a rapid sclerosis and atrophy with no evidence of infection An ascending infection of the pancreatic duct may give rise to a chronic pancreatitis It has been produced experimentally by injecting bacteria into the duct Arteriosclerosis causes chronic pancreatitis Numerous cases have been reported in alcoholics often associated with cirrhosis of the liver In Opie s series of chronic pancreatitis cirrhosis was present in over 25 per cent

Symptoms of Chronic Pancreatitis

According to the writer s view Bloomfield (1934) is right in stating that chronic pancreatitis is a vague entity as a rule not clearly recognizable during life At autopsy a certain amount of fibrosis usually detectable only with the microscope is found in a good many elderly people but it is doubtful if this leads to any clinical symptoms In dogs kept alive a year or more after producing extreme sclerosis and atrophy they seemed free from symptoms except those due to the absence of pancreatic juice namely large frequent stools containing much fat and undigested meat with resulting loss of weight They never gave any indication of suffering pain which some clinical writers say is present in half or more of the cases of chronic pancreatitis Rarely has the clinical diagnosis of chronic pancreatitis been confirmed by autopsy Most of the cases of fatty diarrhea with the characteristics of pancreatic insufficiency prove to be cancer involving the pancreas

Treatment of Chronic Pancreatitis

Chronic pancreatitis characterized by the formation of fibrous tissue is no more curable than is chronic nephritis or cirrhosis of the liver The proper diet can be determined only after a careful examination of the feces If the stools contain much fat and many muscle fibers a diet low in fat and protein should be given Milk is better absorbed than other

Chronic pancreatitis certainly is a rare condition Among 20 000 post mortem examinations performed during forty one years at Guy s Hospital London there were only 4 cases of chronic interstitial pancreatitis made out on naked eye examination only one of which was undoubted

In spite of the fact that the surgeons have made the diagnosis of chronic pancreatitis by palpation in many cases in very few of these has the diagnosis been confirmed at autopsy Koerte has reported an undoubted case There was severe pain and icterus of seven months duration The gall bladder contained 1 200 c c of clear yellowish fluid There were no stones in the biliary ducts or gall bladder The common duct and the main pancreatic duct were occluded by a tumor in the head of the pancreas the size of a small apple Koerte made a diagnosis of obstruction of the ductus choledochus due to pancreatic carcinoma The patient died and the tumor on microscopic examination was found to be localized chronic interstitial pancreatitis and not a carcinoma as had been diagnosed during life

Diagnosis of chronic pancreatitis by the surgeon at operation is open to criticism He bases it on the palpation of an enlarged and hard pancreas but palpation of the pancreas in operation on the common bile duct is difficult and often untrustworthy A hard pancreas is not necessarily a diseased pancreas and no organ normally varies more in size than the pancreas In several cases in which experienced surgeons have assured me that undoubted chronic fibrosis of the head of the pancreas existed the autopsy a few days later showed no swelling or other pathological condition in the pancreas Undoubtedly chronic fibrosis of the head of the pancreas by pressure may produce occlusion of the common bile duct with resulting jaundice but Mayo Robson s claim that this is of frequent occurrence cannot be accepted The facts indicate that jaundice due to pressure in cases of chronic pancreatitis is very rare Opie records only one case that described by Pourtoy in which a sharply localized focus of sclerosis of obscure origin had caused constriction of the common bile duct with jaundice The undoubted case of Koerte has been described already Opie (1910) says Jaundice with acute or chronic inflammation of the pancreas is in most instances adequately explained by cholelithiasis or other hepatic disease preceding or accompanying the pancreatic lesions Heiberg (1914) gives in his text book an able discussion of the relation of chronic pancreatitis to obstructive jaundice and arrives at the same conclusion The pancreatic swellings associated with biliary disease usually are due to acute interstitial edema and generally subside quickly although they may progress to a toxic necrosis

Etiology and Pathological Anatomy of Pancreatic Calculi

Bacterial infection of the pancreatic ducts with stasis of the flow of secretion due to obstruction leads to the formation of pancreatic calculi Stone formation is the most important complication of inflammation of the duct the so called wirsungitis The view that stones arise in ducts that are free from inflammation is untenable for the following reason The stones are rich in calcium The normal pancreatic juice is free of calcium Hence inflammatory processes precede the formation of calculi (Katsch and Brinck 1938) They are found often in association with biliary calculi

The calculi may occur singly but usually are multiple and may be present in great number Carnot counted 300 stones in one case They are grayish white of soft consistence and friable round rough and coral like They may be very small resembling a coarse powder and rarely are larger than a cherry stone They are composed of calcium phosphate and calcium carbonate intermixed with organic substance The stones usually lie near the opening of the main duct By obstructing the flow of secretion they lead to atrophy of the acini and sclerosis of the gland The ducts often are dilated

Symptoms of Pancreatic Calculi

A clear clinical picture of pancreatic calculi is lacking Diabetes i frequent It was present in 36 of 80 cases collected by Lazarus (1906) A glucose tolerance test should be made in all suspected cases Symptoms of obstruction of the pancreatic ducts may occur If the main duct is occluded completely rapid atrophy of the gland takes place It is possible for a stone to cause jaundice by pressure on the common bile duct. Gould (1898) reported an instance of this There may be periodic attacks of colic. These may be indistinguishable from biliary colic but in some instances the pain and tenderness have been below the left costal border Signs of obstruction of the duct should be sought but suggestive disturbances of digestion are more common than creatorrhea and steatorrhea A definite diagnosis has been made by finding calculi in the stools in a number of cases The feces should be examined with the patient on a test diet The stones usually are small and in order not to overlook them all the feces collected during the period of examination should be passed through a sieve Absence of bilirubin and cholesterin distinguishes them from gallstones From the stools of Kinnicutt's (190-) patient both pancreatic and biliary calculi were recovered but the

food containing fat and protein Unabsorbed split fat makes the intestinal contents acid and thus irritates the epithelium All meat must be cooked thoroughly and chopped finely Gelatin is a good substitute for meat It is easily digested by pancreatic juice and its hydrolytic products do not easily undergo putrefaction Sugar and farinaceous foods are well absorbed even in serious cases Arrowroot sago and rice are to be used If there is glycosuria do not reduce the carbohydrate of the diet but depend upon insulin Vegetables must be given cautiously as the power to dissolve cellulose is lessened Pancreatic ferments in large doses are beneficial sometimes Pancreatin should be given thirty minutes to one hour after meals If there is achylia gastrica dilute HCl should be taken with each meal

Pancreatic Infantilism

In one of my dogs in which the pancreatic ducts were tied when a puppy sexual development did not take place Although she lived to be nearly three years old she looked and acted like a puppy She never menstruated and at autopsy the ovaries were undeveloped Bramwell (1904) reported a case of fatty diarrhea lasting nine years in a boy of eighteen whose physical development was arrested at the age of ten After pancreatic extract was given the diarrhea was checked and there was a rapid increase in weight with development of the sexual organs previously in an infantile state Two similar cases have been described by Thompson and one by Rentoul (1904) Langdon Brown (1905) reported a case of fatty diarrhea and infantilism in a boy of sixteen with congenital syphilis Chronic pancreatitis was found at autopsy

Pancreatic Calculi (Sialolithiasis)

Stones in the pancreatic ducts rarely have been diagnosed during life and rarely found at autopsy Among 24 314 autopsies collected by Mockel pancreatic calculi were found only 6 times Ludin (1938) in the space of three years diagnosed 4 cases in vivo by roentgen films which were confirmed by autopsy He then determined to make a systematic search and made a routine x ray picture of the pancreas removed at every autopsy at the Basel pathological institute When stones were found a microscopic examination was made In examining 542 pancreatic glands stones were found 28 times or about 5 per cent varying in size from the head of a pin to a hazel nut He believes that they are the cause of many instances of unexplained pain in the upper abdomen

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attacks of pain were all typical of biliary colic Attacks of pain which have been present in 70 per cent of the cases (Loeffler 1938) lead to the mistaken diagnosis of peptic ulcer or gallstones When in addition to pain there is marked loss of weight with diarrhea it is a natural error to regard the case as cancer of the pancreas (Loeper and Bioy 1936) Gulcke (1924) was able to find only 15 cases reported in which the correct diagnosis had been made during life

Treatment of Pancreatic Calculi

In a search of the literature Schmieden (1927) found only 36 cases in which stones had been removed at operation Of the last 11 operated on in his series apparently all were cured When the stone lies in the head of the pancreas the surgeon usually has removed it after opening the duodenum When the stone is in the body of the pancreas a direct incision into the organ is necessary This entails the risk of serious hemorrhage and of acute pancreatic necrosis

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CHAPTER IX

DISEASES OF THE PERITONEUM

BY M. C. LINCOLNS AND THOS. R. BOGGS

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from contiguous infected tissues in the body (endogenous local infection) (c) from remote foci of infection in the body (endogenous metastatic infection)

It is convenient to discuss the pathogenesis of peritonitis under these three headings

(a) *Exogenous Infection of the Peritoneum* —Penetrating wounds of the abdominal wall (traumatic or surgical) furnish the opportunity for infection of the peritoneum by bacteria from outside the body The number and character of the organisms thus carried in determine to some extent whether or not the powers of resistance of the peritoneum will be overcome and a peritonitis result A second factor of great importance is the amount of coincident injury to the peritoneal surfaces and the degree to which foreign material (bits of clothing fragments of shell gravel etc) has lodged within the peritoneal cavity The patient s level of resistance at the time of the injury must likewise be of importance in determining the outcome The estimation of the e factors in individual cases is difficult prediction as to the occurrence or character of peritonitis in simple perforating abdominal wounds is accordingly most uncertain

(b) *Endogenous Local Infection of the Peritoneum* —Bacteria in organs or tissues contiguous to the peritoneum give rise to peritonitis by two mechanisms simple extension of the bacterial growth through the peritoneal membrane and by rupture or perforation of the peritoneal membrane with an inpouring of infective material

The resistance of the parietal peritoneum to penetration by bacterial growth is much greater than that of the visceral peritoneal membrane Retroperitoneal abscesses and abscesses in the anterior abdominal wall frequently lie in intimate contact with the peritoneum without extending through to the peritoneal cavity and conversely it is relatively infrequent that a purulent peritonitis gives rise to extraperitoneal abscess The visceral peritoneal layer which covers the digestive tube biliary tracts liver spleen etc is much less resistant and infection in these viscera spreads readily to the peritoneal cavity

A rupture of the peritoneal membrane leading to inflow of infective material from contiguous organs or tissues may be due to trauma (as in perforation of the intestine by a stab wound) or it may be due to destruction of the membrane by a disease process Ulceration and gangrene of the walls of the hollow viscera are frequent causes of perforation of the peritoneal membrane Inflammatory infiltration of the peritoneum renders it more friable and even when not actually necrotic it may readily be ruptured if subjected to mechanical strain (intraintestinal gas pressure peristaltic movements pressure of confined exudates as for instance pus in the appendix or gall bladder)

The diseases of the peritoneum are conveniently classified for clinical description in the following groups

1 Non Tuberculous Peritonitis
2 Tuberculous Peritonitis
3 Echinococcus Disease of the Peritoneum
4 Tumors of the Peritoneum

Peritonitis (Non Tuberculous)

The three great serous cavities of the human body which are derived from the embryonic coelomic cavity the pleura the pericardium and the peritoneum show a marked similarity in their reaction to infection Their community of origin and their likeness in structure are reflected to a considerable extent in the character of the pathological processes which occur in each In each there is a tendency to a rapid diffusion throughout the cavity of the infecting agent a capacity for the quick outpouring of large exudates a possibility of almost equally rapid absorption an early formation of fibrinous adhesions tending to localize the infectious process and a later fibrous organization of the inflammatory products

Of the three large serous cavities however the peritoneum is that which by its anatomical relations is subject to infection from the greatest variety of sources for it is in intimate contact with the bacteria laden digestive canal and with the liver gall ducts gall bladder spleen kidneys ureters urinary bladder and in women the internal genitalia Infection in any of these organs is therefore attended with at least the possibility of a consecutive peritonitis With the other serous cavities also it shares the likelihood of infections of hematogenous and metastatic origin or by perforating wounds

Etiology of Peritonitis

There are three main sources from which bacteria causing peritoneal infection are derived (a) from outside the body (exogenous infection) (b)

with a bacteriemia of the same organisms but in which a primary focus is not demonstrable Many authors however prefer to call such cases idiopathic

It is of practical significance to bear in mind the relative importance of the various starting points of acute peritonitis In 446 cases of acute diffuse peritonitis examined after death Benda found that the appendix was the *starting point in 115 cases the stomach and duodenum in 68 the rest of the* intestine in 118 the female genitalia in 81 the gall bladder in 10 the kidney and urinary bladder in 10 the pancreas in 2 the spleen in 1 4 were post operative 2 hematogenous and 35 of unknown origin

Bacteriology

It is apparent today that a complete classification of peritoneal infections according to the causative bacteria is not feasible In only a relatively restricted number of cases in the first place are we safe in assuming that a single organism is the responsible cause of the peritonitis The infections of gastrointestinal origin which constitute a large majority of all cases of peritonitis are for the greater part mixed infections in which the relative *importance of the various species present has not been determined* with certainty Moreover both in the mixed and in certain of the pure infections the evolution of the disease is influenced more by the mode of occurrence (perforative traumatic etc) the point of entry the general condition of the patient etc than by any detectable specific qualities of the organisms present This is sufficient to take away any value from a purely bacteriological classification

However there remain three types of infection whose total percentage of incidence is not inconsiderable which are due to specific organisms usually present in pure culture In these types the pathological and clinical picture is *apparently determined by specific characteristics of the causative* organism They will accordingly be described later on as pneumococcic streptococcic and gonococcic peritonitis The general relations of the common bacteria to peritoneal infection will be briefly discussed at this point

The variety of bacteria concerned is very great In the earlier days of bacteriological investigation of peritonitis the bacillus coli was the organism most frequently isolated It soon became apparent however that this was due to the facility with which this organism overgrew other organisms in the peritoneal cavity and on the usual nutrient media Study of cover slip preparations *from peritoneal exudate shows a varied flora* in almost all cases of peritonitis arising from the digestive tract Investigation of very early cases cultures made from the edge of a spreading infection

Disease processes which by the above mechanisms of extension or perforation give rise to peritonitis may be situated in the gastrointestinal tract in the adnexa of this tract (liver biliary tract and pancreas) in the urinary tract (kidneys ureters, bladder) in the internal genitalia (tubes uterus ovaries seminal vesicles prostate) in the abdominal lymph glands or lymphatic vessels, in the supporting tissues (muscle fascia bone) which bound the abdominal cavity in the spleen in the adrenals or in the abdominal blood vessels Of the many possible sources of endogenous local infection of the peritoneum just mentioned the first four are much the most important The specific disease processes occurring in these tracts which most commonly give rise to peritonitis by extension or perforation are the following

The gastrointestinal tract

Appendicitis
Ulcer of the stomach
Ulcer of the duodenum
Typhoid ulcer of ileum or colon
Tuberculous dysenteric cancerous uremic ulcerations
Intestinal obstruction (volvulus intussusception strangulation)
Intestinal infarction
Diverticulitis

The adnexa of the gastrointestinal tract (liver and biliary tract pancreas and pancreatic ducts)

Acute and chronic cholecystitis with or without cholelithiasis
Impacted gallstone in the common duct with cholangitis
Abscess of the liver
Acute pancreatitis

The internal genitalia

Acute and chronic salpingitis
Acute metritis
Infected myomata
Acute prostatic abscess
Seminal vesiculitis

The urinary tracts

Perinephric abscess
Rupture of the infected urinary bladder

(c) *Endogenous Metastatic Infection of the Peritoneum* —Of the cases of peritonitis arising from foci of infection at a distance in the body the most common are those seen in conjunction with streptococcus angina severe erysipelas pneumonia or malignant endocarditis Metastasis in such cases is probably always hematogenous To be similarly classed are those cases of pneumococcal or streptococcal peritonitis apparently associated

the bacillus coli is the predominant organism are usually characterized by an abundant exudate of milky foul smelling pus rich in cells and fibrin

Staphylococcus —Various strains of staphylococci are frequently found in peritoneal infections usually in association with other organisms but not infrequently in relatively pure culture Flexner showed that they were especially frequent in cases of exogenous infection (perforative trauma of the abdominal wall) The staphylococcus aureus was the strain he found in such cases It gives rise to a virulent peritonitis Dudgeon and Sargeant laid stress upon the frequency of occurrence of the white staphylococcus probably Welch's staphylococcus epidermidis albus They believe that this coccus is the earliest invader in a very high percentage of cases of peritonitis Its virulence is low and these investigators believed that its influence was essentially favorable in that a mild initial inflammatory change was set up which rendered the peritoneum more resistant to later and more virulent organisms These findings have not been fully confirmed

Streptococcus —The various strains of streptococci are very frequently found both combined with other organisms and in pure culture The streptococcus pyogenes is probably not a normal inhabitant of the digestive tract and it appears likely that the strain of streptococcus which is commonly found in association with the colon bacillus in peritonitis of digestive tube origin possesses less virulence In smears a streptococcus type of organism may sometimes be seen which is apparently an anaerobe The streptococcus pyogenes causes a most virulent peritonitis the so-called septic peritonitis in which the constitutional symptoms predominate death occurring before the peritoneal infection has given rise to any marked reaction on the part of the peritoneum Types of this form of infection are the peritonitis occurring with septic sore throat post operatively in the puerperium etc

Pneumococcus —Pneumococcus is occasionally found in combination with other organisms in peritonitis of local endogenous origin but it is also a frequent cause of a metastatic infection in which it is found in pure culture The characteristics of this pneumococcic peritonitis will be discussed later under that heading

Gonococcus —Although a local or more rarely a generalized peritonitis has long been known as a common sequel to gonorrheal metritis or salpingitis the role of the gonococcus in these secondary processes was long in doubt as it was not believed that the gonococcus alone could grow within the peritoneal cavity (Treves and Senn) The investigations of Wertheim Menge Sutton and Cushing later proved however that the gonococcus is frequently the cause of a circumscribed or rarely of a diffuse peritonitis The features of this specific peritonitis will be dealt with later

The bacillus proteus faecalis alkaligenes and pyocyaneus have been frequently recovered from purulent peritoneal exudates

careful plating the use of selective media of animal inoculations and of graded anaerobiosis have yielded us knowledge of the occurrence and some idea of the relative frequency of numerous other organisms The various strains of streptococci staphylococci pneumococci the bacillus proteus pyocyaneus and typhosus are the commonest aerobes found in mixed infections while the bacillus ramosus perfringens, tetanoides and aerogenes capsulatus are the most common anaerobes Numbers of other bacteria however are to be seen in smears which have not yet been identified

Bacillus Coli—Though no longer retaining its position as the chief etiological agent in the production of peritonitis, the bacillus coli still holds a predominant position in the bacteriology of peritoneal infections The overwhelming numbers of this organism constantly present in the intestinal tract readily explain its occurrence in the peritonitis following any form of perforation of the digestive tube or of its secondarily infected adnexa (appendix diverticulum biliary tract)

Welch and Ziegler early showed moreover that the bacillus coli possesses the power of transmigration through the damaged intestinal wall thus making clear the mechanism of the occurrence of peritonitis originating about a gangrenous loop of intestine or beginning on the peritoneal surface opposite an ulceration or arising from the congested portion of the bowel in an incarcerated hernia

DeKlecki claims that the bacillus coli recovered from an isolated loop of gut exhibits a heightened virulence Furthermore in many instances the colon bacillus is not the cause of the primary lesion in the intestinal wall but merely passes through the damaged tissues as a secondary invader owing to its power of more rapid transmigration and becomes the primary agent in the consequent peritonitis Thus Curtis has recovered the colon bacillus in pure culture from the pus about a non perforative appendicitis whilst in the appendix wall he demonstrated the streptococcus The invasive power of the colon bacillus is further shown by the fact of its recovery from the blood in a number of cases of peritonitis It is more likely to be found here in the early stages and one of us has grown it from the blood in the first few hours of the sudden incarceration of a large umbilical hernia from which upon reduction no evidence of peritonitis resulted Though the colon bacillus very rapidly overgrows other organisms in the peritoneal cavity in the early stages of an infection in which it is present it shows a tendency also to die out in the later stages Runeberg concludes that the peritoneal cavity is essentially an unfavorable locus for the continued development of this organism It is possible of course that secondary invaders may determine conditions unfavorable to its growth

Dudgeon and Sargeant have shown that the bacillus coli will not grow in the presence of the bacillus pyocyaneus Cases of peritonitis in which

of the organisms due apparently to the bacteriolytic properties of the normal peritoneal fluid and to phagocytosis by the normally present cells If however a large number of organisms have been injected many will escape immediate destruction Certain virulent strains moreover show greater resistance There ensues almost immediately an outpouring of serofibrinous exudate which deposits a fine fibrinous network on the involved peritoneal surfaces and on the omentum In this network the bacteria and cells are largely deposited so that examination of the free fluid at this time shows relatively few organisms and a leukopenia From the fibrin layer however viable organisms may be recovered Further exudation occurs in which polymorphonuclear leukocytes derived from the blood become increasingly more numerous These cells are actively phagocytic and they perform this function more effectively in the fibrin layers than in the free fluid Their arrival in considerable quantities may complete the destruction of the bacteria reinforced as it is by the renewed bacteriolytic power of the fresh exudate The efficiency of these two methods of defense is a measure of the bodily resistance and as in all infections the outcome is dependent both upon the ability of the body to produce antibodies and marshal leukocytes and upon the virulence and dosage of the organisms involved Bordet has shown in the instance of streptococcic peritonitis in guinea pigs that the successive generations of the organisms developing in the peritoneal cavity become more and more resistant and that an evidence of this is apparently the development of demonstrable capsules on the part of these resistant organisms The presence of blood clot or traumatized or necrotic tissues in the abdominal cavity may serve as a protection to the bacteria from the free action of the bactericidal exudate and so act as a nidus for the growth of more resistant strains

When in animals the infection has continued for about twenty four hours there appear in the exudate in addition to the microphages numbers of macrophages large mononuclear cells derived most probably from the proliferation of endothelial cells of the peritoneal wall or of the subserous lymphatics They are very actively phagocytic and play a considerable role in the final resorption of the inflammatory products in such cases as recover

In animals there is an initial rapid resorption of the organisms from the peritoneal cavity chiefly through the diaphragmatic lymphatics It is signalized by a bacteriemia and by the swelling and engorgement of the mediastinal lymph glands The resultant deposition of bacteria in various organs may lead to the development of metastatic foci In man the picture exhibits more variety because of the varied methods of infection but it follows in its main lines what has been above described Since the commoner methods of infection are more gradual there is less frequently an

Anaerobic Organisms —The investigations of Heyde Veillon and Zuber and of Runeberg drew attention to the importance of the anaerobic organisms in peritoneal pathology The bacillus fragilis ramosus perfringens tetanoides fusiformis and mucosus were isolated The cases investigated were mostly those of appendiceal peritonitis In twenty two cases of peri appendiceal suppuration Veillon and Zuber found anaerobes nineteen times associated as the predominating organism with colon bacilli and streptococci and twice found anaerobes in pure culture These authors attribute the gangrene of the appendix and the fetor of the pus in such cases to specific properties of the anaerobes Ikonikoff has shown that the anaerobes pass through the wall of an experimentally strangulated loop of intestine far more quickly than do the aerobic organisms The toxines of these organisms according to Runeberg reproduce the constitutional effects of peritoneal infection They are not found in the blood stream Later workers have not altogether confirmed the importance attributed to the anaerobic bacilli in the etiology of appendicitis Their influence upon the character of the peritoneal exudate is unquestionable

Pathology

The entrance of pathogenic bacteria into the peritoneal cavity is followed by a varying degree of dissemination depending upon the movements of the diaphragm the peristaltic activity of the intestines and the currents in the normally present peritoneal fluid The peritoneal membrane wherever involved responds to the irritant action of the bacterial toxins by a local hyperemia by edema of the superficial layers of cells and by exudation The character of this exudate depends to a considerable extent upon the type and number of organisms present and upon the presence or absence of other foreign and irritant matter (gastric juice intestinal contents bile etc) The early exudate is serous or serofibrinous and in the milder infections it may remain so or in the most fulminant varieties death may occur before any further peritoneal reaction has resulted In the usual case of diffuse peritonitis however the early serofibrinous exudate tends to become purulent or fibrinopurulent and the presence of foreign matter from the intestinal tract hastens this change In certain cases seen at the time when a partially circumscribed infection is gradually spreading one may find a purulent exudate at the point of origin of the process while elsewhere the fluid is still serofibrinous

The role of this inflammatory exudate is protective The mechanism of the protection has been elucidated to some extent by the study of experimental peritonitis In the experimental animals the injection of bacteria into the peritoneal cavity is followed by a rapid destruction of many

peritoneal cavity are the next gross changes seen and they are accompanied by an increase in congestion and edema of the membranes With the increase of the fibrin deposits the coils of intestines mesentery omentum etc become glued together either by direct adhesion or by uniting membranes and bands The increased fluid exudate collects at first in the loins or pelvis but as the matting together of the intestines by adhesions proceeds pockets are formed filled with fluid exudate The character of the exudate usually changes rapidly from serofibrinous to purulent To some extent the nature of the exudate is determined by the type of the causative organisms The exudate in virulent streptococcic infections is often a rather thin brownish fluid In infections due chiefly to the bacillus coli a thick creamy stinking pus is usually found Pneumococcus infections are characterized by a great abundance of fibrinous shreds and flakes in a greenish white pus with thick deposits of false membrane on all the involved surfaces

In cases of peritonitis which tend towards healing regressive processes take place consisting primarily of absorption or organization Serous exudates are absorbed directly and purulent exudates are absorbed after autolytic liquefaction of their cellular and fibrinous elements Where the endothelial surface of the peritoneum has been destroyed the overlying fibrinous adhesions are invaded by connective tissue upgrowth and thus are transformed into more or less permanent fibrous bands Fixation and distortion of viscera by such bands occur and not infrequently partial or absolute intestinal obstruction Superficial adhesions between surfaces whose endothelium has survived are usually completely absorbed Large localized collections of pus not infrequently resist absorption in this event they may find an exit by perforating through the abdominal wall or into the lumen of the intestine or they may become encapsulated and remain as putty like masses in the midst of adherent coils of intestine and fibrous tissue Calcification of such masses may occur

Symptomatology of Peritonitis

The symptoms of acute peritonitis develop in a sequence which corresponds to the sequence of the pathological changes occurring within the peritoneal cavity and to their successive effects upon the bodily functions The variability of the factors involved the condition of the patient the mode of infection the virulence of the infection itself alter markedly in individual cases the clinical picture which the patient presents to the physician In general however a sufficient analysis will serve to differentiate the symptomatology of the following stages in acute peritoneal infection the two early stages *i e* the stage of onset and the stage of spreading and

initial bacteriemia though perhaps very early blood cultures would show that it is more frequently present than has been thought

The more gradual onset also changes the picture in that it permits another protective measure to assume prominence the tendency to encapsulation The fibrinous deposit upon the peritoneal surfaces results in loops of gut, omentum and mesentery readily adhering to form a matted mass which may effectively wall off the infected area The quiescence of the intestine is a prime factor in securing an early circumscription of the process by adhesions The role of the omentum is an important one also in walling off the infected area It is not known by what means the omentum progresses towards the point of infection but in a majority of instances it will be found early adherent in the neighborhood of the primary focus

While theoretically the resorptive power of the peritoneum must be viewed as a protective mechanism it is in fact the chief cause of death in fatal peritonitis Rapid absorption of bacteria through the diaphragmatic lymphatics is apparently soon checked by the blocking of these channels by edema and inflammatory debris but the bacterial toxins freed within the peritoneal cavity pass into the blood stream Only when thus absorbed do these toxins cause pathological effects on the vital centers the central nervous system and the heart Opie s investigations led him to believe that resorption is also unfavorable in that it removes the antitrypsin contained in the fluid exudate thus freeing from inhibition the proteolytic powers of the leukocytes and permitting the premature destruction of protective adhesions with consequent diffusion of the infection When a peritoneal infection has been overcome however the resorption of the inflammatory exudate and membranes once more becomes a beneficial function

The gross appearance of the peritoneum depends upon the extent and the stage of the infection The earliest change observed is the congestion of the capillaries and small blood vessels of the peritoneum In rapidly spreading fatal infections this congestion may be diffuse that is it may involve the greater part of the serous surfaces In cases of lesser virulence it may be observed only about the portal of entry of the infection (*e g* the appendix) and spreading irregularly over the exposed surfaces of adjacent coils of intestine mesentery or parietal peritoneum

This vascular dilatation is quickly followed by edema of the superficial cell layers exudation of serous fluid and a fine fibrinous deposit upon the peritoneal surface To the naked eye these changes are seen as a slight dulling of the luster of the affected membrane with a finely granular appearance of its surface The early serous exudate is absorbed almost as quickly as formed

Increase in the fibrin deposits and the appearance of free fluid in the

constitutional symptoms are more attributable to absorption of toxic material than to shock

A moderately acute attack of appendicitis well illustrates in many cases this type of onset of peritonitis It is theoretically true that in such cases at the onset the pathological process is still extraperitoneal but the production of adhesions is evidence of the fact that even very mild attacks produce a localized peritonitis and for clinical purposes it is not wise nor feasible to differentiate the appendiceal and peritoneal stages of the infection

The onset is usually sudden with sharp pain on the right side of the abdomen or frequently in the epigastrium This pain tends slowly to increase in intensity and within a few hours becomes a severe aching which settles more and more definitely in the right lower quadrant of the abdomen Colicky exacerbations may occur On examination the abdominal wall is not rigid but comparative palpation will show greater resistance on the right side especially of the lower segments of the right rectus muscle as compared with the left Tenderness may be generalized but its maximum is usually demonstrable at or about McBurney s point Not infrequently there is well marked cutaneous hyperesthesia in this region Vomiting at the onset *is common* but when the stomach is empty nausea and vomiting usually *cease Constipation is the rule*

If the pain has been severe from the start mild constitutional symptoms of shock may occur As a rule however there is not much prostration But almost from the start of the pain the temperature will begin to rise in most cases to 100 to 102 F a slight chill may occur and the pulse rate is increased (90 to 110) Its quality remains full and strong Even in the first hours a leukocytosis of 12 000 to 15 000 will be found If operation is performed in the first six hours the only signs of peritonitis will be the infection of the peritoneal coat of the swollen appendix and perhaps a slight increase in the peritoneal fluid in the right flank

When peritonitis has begun by one or the other of the above methods of onset various sequelae *may appear* Immediate *regression or healing may take place the process may continue and run its course as a localized peritonitis or a stage of spreading infection may lead to a diffuse peritonitis It is of course* extremely important to differentiate the clinical pictures which indicate these events in the pathological processes and especially to stress the difficulties which may arise in determining whether a process is regressive stationary or spreading All of the physician s acumen will be needed for the task

Regression of the Peritonitis —Regression of the peritoneal inflammation will be accompanied by regression both in the local abdominal symptoms and in the constitutional symptoms attributable to shock and to infection

The pain becomes less diffuse and more limited to the site of the lesion

the two resultant later states of localized peritonitis or of diffuse peritonitis

The stage of onset is characterized by the appearance of the local symptoms of peritoneal irritation and by the constitutional symptoms with which the patient reacts to the shock of such peritoneal irritation and to the early absorption of toxic material At the very first the symptoms of peritoneal irritation are apt to be diffuse even though the pathological process which has given rise to them is still localized and the more acute the process the more apt is one to observe this initial diffuseness of the abdominal symptoms Likewise very early one may observe a preponderance of the constitutional symptoms attributable to shock over those due to infection and it is also true that such constitutional symptoms of shock occur especially when the invasion of the peritoneal cavity has been acute Diffuse abdominal symptoms and symptoms of shock are therefore characteristic of the earliest period of an active invasion of the peritoneum by an infective process

The onset of peritonitis following perforation of a hollow viscus may be taken as a common example of such an association of symptoms Pain is usually the earliest symptom felt by the patient but its appearance is followed almost at once by other abdominal symptoms of peritoneal irritation tenderness rigidity of the abdominal muscles vomiting and constipation The onset of the pain follows the perforation immediately Its intensity is excruciating like a knife in the belly as Dieulafoy has said One must suppose that it is due to the action of the irritating gastric intestinal or biliary contents on the nerve terminals in the parietal peritoneum The distribution of the pain is not well defined the whole abdomen is possessed by it It is constant with acute exacerbations apparently due to colicky contractions of the intestines Any movement increases the suffering and the patient usually assumes an immobile position on his back Cough hiccough vomiting and breathing increase the pain Exquisite sensitiveness to pressure develops almost immediately in such a case The patient can hardly bear the weight of the bed clothes and fears the gentlest touch of the examiner s hand Board like rigidity of the abdominal muscles appears as a reflex attempt of the body to keep at rest the abdominal contents Abdominal breathing ceases the breathing is thoracic in type and shallow Nausea and vomiting are frequent and distressing Constipation from the start is the rule The shock of such an onset expresses itself by the haggard grayish facies chilliness clammy sweat small rapid low tension pulse shallow often irregular breathing weakness restlessness mental distress and apprehension

In peritonitis of more gradual onset the abdominal symptoms of peritoneal irritation show from the start more tendency to be localized or at least to be more marked about the site of the pathological process and the

and may be readily limited in its spread by the natural defensive mechanisms of circumscribing adhesions The anatomical relations at the site of the initial focus of infection may favor or hinder effectual walling off of a beginning peritonitis Experience has shown that the regions of the appendix of the gall bladder and of the pelvis are the most frequent sites of circumscribed peritonitis whereas peritoneal infections beginning in the central region of the abdomen are most apt to become diffuse The virulence of the organism is likewise an important factor A virulent strain of streptococcus reaching the pelvic peritoneum by extension from the puerperal uterus will spread with great rapidity throughout the abdominal cavity whereas gonococcal pelvic peritonitis will rarely fail to become circumscribed The individual resistance of the patient is likewise a factor of undoubted importance but the scope of its action we can only describe by generalities

Prediction in the stage of onset as to the future diffusion or circumscription of a peritoneal infection is at best uncertain and difficult The abdominal symptoms and signs may be localized from the start or if the onset is very acute they may at first be diffuse In the latter case however when the shock of onset has worn off inside of the first twenty four hours there will be sufficient limitation of the pain sensitiveness to pressure and rigidity to mark the site of the focus of infection At this stage the process is best termed a localized peritonitis for evidence that it is definitely circumscribed has not yet developed The best evidence of the walling off of the infection is the development of a palpable mass at the site of the infection and the lack of those signs and symptoms which indicate a spreading infection As opposed to the general regression of abdominal and constitutional symptoms in the case which is tending to immediate subsidence of the pathological process the case in which circumscription of an active process is taking place continues to exhibit fever a rapid pulse leukocytosis a toxic appearance local abdominal pain sensitiveness rigidity constipation often distention and after the first two or three days usually a palpable mass This mass has as a rule indefinite contours and a putty like consistency and occupies the general area of the initial focus of infection The inference as to pus formation in such a circumscribed peritonitis is drawn from a *further rise in the temperature pulse rate and leukocyte count* without evidence of a diffusion of the infection from increase in the local pain due to stretching of the tissues and from exquisite localized tenderness over the site of the abscess The last is to many surgeons the most significant and constant sign If the abscess is a large one *and it may vary in* contents from a few teaspoonfuls of pus to several quarts fluctuation may be obtained Abscesses of long standing may be accompanied by edema of the abdominal wall

and this pain gradually disappears Spontaneous pain first lessens then pain on movement and finally pain on pressure (Hertzler) Muscular rigidity gradually diminishes Nausea disappears and appetite returns The bowels move again spontaneously The temperature and pulse fall to normal levels The leukocytosis subsides The patient's expression indicates comfort and restfulness

As has been pointed out however regression of symptoms may occur which does not indicate a corresponding regression of the underlying pathological process A stormy onset with diffuse abdominal symptoms and a condition of shock is followed by an apparent betterment The pain becomes less diffuse and the sensitiveness and muscular rigidity more limited to the site of the lesion Vomiting ceases The patient recovers from the prostration of the acute onset the color of the face returns the pulse is stronger The physician must be on his guard lest he infer that this recovery from the dramatic symptoms of an acute onset indicates a regression of the pathological process The continued presence of the less striking symptoms attributable to infection must warn him that this is merely a traitorous lull (Dieulafoy) Of these symptoms a rapid pulse and the appearance of the patient are perhaps the most significant In true regression of the pathological process the pulse tends to return to normal limits but where the peritoneal infection is not subsiding it will remain fast 100 to 120 In continued infection also the facies though perhaps less haggard than in the agony of the onset retains an uneasy drawn expression and a certain mental and physical restlessness is apparent Fever and leukocytosis are usually present especially in the less overwhelming infections In the more virulent infections in which fever and leukocytosis may not be present at this stage the pulse and the facies of the patient are especially affected

If in this temporary lull surgical intervention does not solve the problem the most careful observation of symptoms and signs will be needed to interpret the nature of the further developments The process may become firmly circumscribed or a stage of spreading infection may lead shortly to a diffuse peritonitis

Circumscribed Peritonitis—A number of factors come into play in determining whether or not a peritoneal infection becomes circumscribed or continues to spread The pathogenesis of the initial infection obviously is of importance in determining this issue Peritonitis due to free perforation somewhere along the course of the digestive canal is unlikely to become circumscribed because the escaping contents of the stomach or gut carry infection almost at once to a large portion of the peritoneal cavity On the other hand peritonitis arising by extension for instance through the wall of the gall bladder or of the appendix is by its nature localized at the onset

and may be readily limited in its spread by the natural defensive mechanisms of circumscribing adhesions The anatomical relations at the site of the initial focus of infection may favor or hinder effectual walling off of a beginning peritonitis Experience has shown that the regions of the appendix of the gall bladder and of the pelvis are the most frequent sites of circumscribed peritonitis whereas peritoneal infections beginning in the central region of the abdomen are most apt to become diffuse The virulence of the organism is likewise an important factor A virulent strain o streptococcus reaching the pelvic peritoneum by extension from the puerperal uterus will spread with great rapidity throughout the abdominal cavity whereas gonococcal pelvic peritonitis will rarely fail to become circumscribed The individual resistance of the patient is likewise a factor of undoubted importance but the scope of its action we can only describe by generalities

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The prompt drainage by operation of a peritoneal abscess may lead to prompt subsidence of the constitutional symptoms and to local healing. The dense adhesions remaining may later give rise to troublesome sequelae. There is always danger however that operation may lead to diffusion of the infection. An unoperated abscess which does not progress runs as a rule a long course. The pain gradually subsides. Diarrhea may alternate with constipation. Intestinal obstruction often develops. The patient may die worn out from fever, toxemia and malnutrition or may eventually overcome the infection. The evacuation of a peritoneal abscess to the exterior is far less frequent than evacuation into the general peritoneal cavity or into the gut. There may be a sudden rupture of the abscess wall or a gradual leakage of pus through crevices. When the latter occurs the development of a spreading infection may be clinically quite insidious. Sudden rupture into the peritoneal cavity is usually accompanied by a sharp fall in temperature and temporary complete relief from pain. The pulse remains fast however and the patient's appearance shows no improvement. Evidence of spreading infection develops rapidly. Rupture into the gut on the other hand is accompanied by sudden improvement in all the constitutional as well as local symptoms.

Spreading Peritonitis.—There are two conditions in which the stage of spreading infection can usually be distinguished clinically: (1) where the peritonitis spreads gradually from the site of the initial lesion until by extension it has become a diffuse process and the clinical picture of the onset and of the lull that follows it is succeeded by symptoms and signs indicative of its gradual extension; (2) where in a case of peritonitis a secondary accident occurs in the initial pathological process (perforation of the infected appendix or gall bladder, gangrene, rupture of a peritoneal abscess). This accident will give rise to a change in the clinical picture which will have as its sequence again the symptoms and signs indicative of rapid extension of the peritoneal infection. In general therefore under the first condition the development of the spreading infection is apt to be more gradual and clinically insidious, whereas in the second condition it will usually be ushered in by an abrupt change in the clinical picture.

The gradual spread of peritonitis is usually accompanied by diffusion of the pain to a more extensive area though the pain is not necessarily increased. In estimating the degree of spontaneous pain the condition and temperament of the patient should always be considered. In cases which are markedly toxic the predominance of pain as a symptom is not to be expected and in highly nervous patients the complaint of pain alone without other evidence should not be accorded undue weight. This generalization of the pain is not constant and there are cases in which no pain is complained of though other evidence points to a rapidly spreading infection. The area of sensi-

tiveness to pressure likewise enlarges This is a somewhat more constant sign An increased area of muscular rigidity will usually be found unless marked distention occurring early has masked it Increasing distention is in itself good evidence of a spreading process and should be carefully watched for It must not be forgotten however that the most grave infections which rapidly overwhelm the patient may run their course with a retracted abdomen

With increasing distention the abdomen becomes more rounded the flanks fill out the percussion note is tympanitic The obliteration of the hepatic dullness by this tympany is when observed a sign of some value Likewise the appearance of a friction rub along the right costal margin is good evidence of the extension of the exudate to the diaphragmatic surface of the liver

The reappearance of vomiting is a grave sign indicative of diffusion of the infection Hiccough has a similar significance Persistent constipation is the rule but diarrhea may occur in spreading peritonitis especially perhaps when the initial process arises from the pelvic organs A gradual ascent in the temperature is common to both diffusing peritonitis and to localized suppuration Fever however is the least dependable of symptoms The pulse shows more constant characteristics an increasing pulse rate is a most valuable indication of a spreading infection As the rate increases the pulse tends to become smaller snappy and hard Its quality however depends largely upon the condition of the patient An increasing leukocytosis is common to spreading infections and to localized suppuration, being perhaps more frequent in the latter The more virulent forms of peritonitis frequently show a leukopenia The general appearance of the patient in spreading infection is indicative of serious illness of anxiety and of restlessness While the cheeks may show a dark flush the eyes are sunken and there is a grayish pinched look about the alae of the nose The patient lies on his back propped up maintaining the trunk immobile but often restlessly moving the arms or turning the head

As has been noted above the extension of peritonitis frequently does not progress gradually from the onset of the disease but dates from the sudden occurrence of a secondary complication such as perforation gangrene or the rupture of a localized abscess The diagnosis of such a complication occurring in the course of the disease may present the gravest difficulties and if it is delayed until confirmed by evidences of a rapidly spreading peritonitis the most favorable moment for surgical intervention may be lost In general sudden changes in the character of the pain in the height of the fever in the quality of the pulse or in the general condition of the patient are ominous signs of intra abdominal catastrophe Sudden relief from localized pain without improvement in the general condition suggest strongly the occurrence of gangrene If evidences of localized abscess are

present accompanied by local pain the sudden relief of the pain will suggest rupture of the abscess If the accumulation ruptures into the free peritoneal cavity the temperature drops to subnormal and the pulse mounts if elsewhere as an appendiceal abscess into the gut, the temperature does not become subnormal and the pulse rate also drops (Hertzler)

A sudden marked increase in pain with secondary appearance of shock (falling temperature rapid thready pulse cyanosis cold extremities) is most suggestive of the occurrence of perforation Such sudden changes in the clinical picture are but too often preludes to the appearance of the symptoms and signs of a rapidly spreading infection

Diffuse Peritonitis —The stage of diffuse peritonitis may be reached as has been seen as a sequence of varying clinical pictures It may succeed practically at once the dramatic onset with shock and diffuse abdominal symptoms due to a free perforation of a hollow viscus into the abdominal cavity Or such a stormy onset may be followed by apparent improvement with localization of the abdominal symptoms and then later evidence of spread of the process may appear and finally the picture of diffuse peritonitis be established Or a gradual onset with well localized symptoms may be followed by sudden great pain and shock evidence of perforation and the picture of a spreading and then of diffuse peritonitis rapidly develop Or in very toxic or cachectic individuals the onset may be so symptomless as to be overlooked and diffuse peritonitis be found only when some symptom such as distention or vomiting attracts attention to the abdomen

It must be remembered that the pathology of diffuse peritonitis includes several types In very virulent fatal infection the whole peritoneum will be found dark brownish purple the coils of intestines are distended and their surface vessels injected the exudate is limited to a few ounces of brownish serous fluid in the dependent hollows This is the type found especially in streptococcus infections and it is usually known as *diffuse* septic peritonitis The term septic refers to the outstanding feature of the patient s condition in this form of peritoneal infection In less virulent and less rapidly spreading infections a diffuse purulent peritonitis may be the end result A varying quantity of white greenish, or creamy colored, purulent exudate occupies the peritoneal cavity The attempts at localization are shown by more or less fibrinous adhesion between the omentum intestinal coils and mesentery Mickulicz has drawn attention to a less acute form of purulent peritonitis characterized by repeated incomplete encapsulation of the purulent exudate so that the peritoneal cavity eventually is subdivided into numerous partly walled off accumulations of pus To this type the name progressive fibrinopurulent peritonitis has been applied Senn Treves and Henrotin have differentiated a form of general peritonitis usually following appendicitis characterized by abundant fibrino-

plastic exudate walling off pockets of serous effusion indiscriminately situated in various parts of the abdomen and accompanied by great distention of the intestines vomiting and frequently alternating constipation and diarrhea If the stages of onset and of spreading have been closely followed the existence of one or the other of the above pathological pictures may often be predicted before operation in a case of diffuse peritonitis From the clinical picture presented by the patient already in the stage of diffuse peritonitis such a differentiation cannot be made with any certainty The manifest toxic state of the patient and the rapidly fatal course (three to four days) however usually will enable one to differentiate the diffuse septic peritonitis from the other types of lesser virulence

The patient with diffuse peritonitis usually lies in the dorsal decubitus with the knees somewhat drawn up The face is drawn anxious with hollow bright eyes and dusky skin and a look of mortal illness A mild delirium is not uncommon An uneasy restlessness is the rule with sleeplessness at night The tongue is usually dry and coated The respirations are somewhat hurried shallow and often irregular The pulse is fast 110 to 130 small and snappy while the patient maintains his resistance but filiform and running as the end approaches The temperature is very variable usually remittent between 101 and 103°F but it may not in some cases surpass 100 F while in others a hyperpyrexia occurs The degree of fever is of little value in prognosis The excretion of urine is usually much decreased Thirst is a constant complaint

The abdomen is distended and rounded It takes no part in the respiratory movements Spontaneous pain in the abdomen is usually diffuse It is less severe than at the onset and colicky exacerbations are less frequent Sensitiveness on pressure may be exquisite but is usually moderate and diffuse Careful palpation may show greater sensitiveness and a mass at the site of the initial focus especially in the less acute cases Rigidity has yielded to the distention The percussion note is tympanitic but usually more so in some areas than in others Shifting dullness in the flanks is rarely to be made out High rectal tenderness and a fullness in the cul de sac may be noted There is absolute cessation of fecal movements and of the passage of gas Vomiting is frequent but is no longer violent The vomitus is usually a greenish fluid but later takes on a brownish tinge It may be blood tinged or contain fecal matter

As a fatal termination approaches the patient may sink into a stupor but frequently a curious and distressing mental clarity and calm succeed the earlier unrest The extremities cool and a cold sweat breaks out on the face The pulse is feeble and running The vomiting becomes a mere effortless regurgitation and often ceases in the last hours The pain disappears Death is often quite sudden

Clinical Types of Acute Peritonitis

A few words may be said of certain types of peritonitis commonly met with which are characterized by their association with a definite initial lesion or with a definite causal microorganism Of such a nature are (a) appendiceal peritonitis (b) perforative peritonitis (c) biliary peritonitis (d) gonococcus peritonitis (e) pneumococcus peritonitis (f) streptococcus peritonitis

(a) *Appendiceal peritonitis* leads all other varieties of peritonitis in frequency The pathology of the peritoneal lesions secondary to appendicitis runs the entire gamut of peritoneal reactions to infection The commonest types seen are (1) circumscribed fibrinoplastic peritonitis (2) circumscribed purulent peritonitis (peritoneal abscess) Its commonest situation is in the right iliac fossa but it may be in the pelvis retrocecal, or subphrenic (3) diffuse purulent peritonitis The multilocular progressive purulent peritonitis of Mickulicz is commonly of appendiceal origin, (4) diffuse septic peritonitis The varying pathology of the appendiceal lesion (catarrhal interstitial suppurative perforative gangrenous appendicitis) and its varying bacterial flora explain in part this complexity in the consequent peritoneal pathology In general it is unwise to attempt to distinguish in the clinical picture an appendiceal and a peritoneal stage Hyperacute cases (usually accompanied by early gangrene of the appendix) show evidences of a diffuse septic peritonitis within the first few hours and lead to death frequently within a day In such cases there is often little to point to the appendix as the point of origin of the process The clinical picture of the less virulent cases usually shows after the first few hours a well marked localization of the symptoms to the right lower quadrant The pain in the first few hours is often diffuse and chiefly in the epigastric region The secondary occurrence of perforation or gangrene of the appendix with ensuing rapid spread of the previously localized peritoneal infection is a characteristic event in the clinical picture of appendicitis The possibility of such a catastrophe must be constantly present in the mind of the physician no matter how mild the onset of an appendicitis may appear On the whole however barring the primarily virulent cases and the occurrence of secondary accidents perforation or gangrene appendiceal peritonitis shows a marked tendency to become circumscribed with or without abscess formation In such cases in twenty four to seventy two hours after onset a mass can usually be palpated in the right iliac fossa If there is pus formation a secondary rupture of the abscess must be expected unless surgically drained If there is no pus formation the process will probably subside leaving a scarred appendix surrounded by adhesions The reflex gastrointestinal genital and vesical disturbances due to this residuum and complicated from

time to time by recurrent acute and subacute exacerbations of the appendiceal infection constitute the clinical picture of chronic appendicitis

(b) *Perforative Peritonitis*—Perforation of a hollow viscus with discharge of its contents into the peritoneal cavity is the commonest cause of acute diffuse peritonitis In a certain number of cases however such a perforation results only in a circumscribed peritoneal infection This is more apt to be the case (a) when prior to the perforation peritoneal reaction about the site of the lesion has led to circumscribing adhesions (b) when the contents of the viscus are small in amount or of slight infectivity (c) when the natural anatomical structures about the site of the perforation tend to resist mechanically the diffusion of the septic material

The appendix is peculiarly *subject to chronic infection with periappendiceal adhesions* Its situation anatomically is favorable to the walling off of infection by the cecum mesentery ileum omentum and parietal peritoneum *These factors explain in part why perforation of the* appendix leads so often to a circumscribed peritonitis W J Mayo estimated that perhaps seventy per cent of patients with acute perforation of the appendix might recover spontaneously A sudden perforation due to virulent infection of a previously normal appendix leads inevitably however to diffuse peritonitis and in no individual case in which perforation is diagnosed or suspected can one safely assume that any other outcome than diffuse peritonitis will ensue

Perforation of the duodenum into the peritoneal cavity is of frequent occurrence It may result from an acute or a chronic duodenal ulceration In the latter case a preexisting periduodenitis with adhesions may limit its diffusion In any case the duodenal contents are usually small in amount and not virulently infective The gall bladder transverse colon and gastrohepatic omentum tend naturally to limit the immediate spread of the extravasated duodenal contents There is no doubt that small duodenal perforations frequently give rise to only circumscribed peritonitis the perforation itself being closed early by plastic exudate Far more usually these natural protections merely delay the diffusion of the peritonitis Such a circumscribed peritonitis may develop into a peritoneal abscess which usually occupies the space under the liver or between the liver and diaphragm *posteriorly or anteriorly (subphrenic abscess)* W J Mayo has drawn attention to the tendency for the infection to spread laterally and down to the appendix region giving rise to a mistaken diagnosis of appendicitis

The tendency to chronicity of gall bladder infection results in the frequent presence of pericholecystic adhesions prior to perforation of the viscus Perforation not infrequently takes place as a sequel of necrosis due to impacted stone in such cases the contents of the gall bladder may

be only mildly infective. The overlying liver, the transverse colon and its mesentery, the omentum and the parietal peritoneum form natural limiting protection barriers. With bacteria of lesser virulence only in the gall bladder contents, spontaneous limitation of the peritoneal infection is a possibility. Early operation gives an excellent prospect if the field is not densely filled with old adhesions. But over against this type of gall bladder perforation must be placed the somewhat less frequent acute phlegmonous cholecystitis with perforation directly following gangrene. Early and fatal diffuse peritonitis is its natural sequel.

Perforations of the small intestines are usually a result of acute ulcerative processes and though some reactive inflammation on the peritoneal surface of the gut may precede the perforation, protective adhesions to neighboring structures are but rarely formed because of the mobility of the coils of gut. The contents of the gut are usually considerable in amount and highly infective. The central area of the abdomen has anatomically the least hindrances to diffusion of the extravasated material. Acute perforations of the small intestines (typhoid ulcers, trauma, dysenteric ulcers) lead therefore to a diffuse peritonitis with less chance of circumscription and less period of delay in its development than is the case in any other type of perforative peritonitis.

Ulcers of the pylorus and of the posterior surface of the stomach resemble duodenal ulcers in their anatomical predisposition to circumscribed infection in case they perforate. They vary, however, in that the contents of the stomach are greater in amount than those of the duodenum. These perforations similarly to those of the duodenum frequently lead to subphrenic abscesses. Perforation of the anterior wall of the stomach has the least chance of limination by natural barriers. Fortunately it is rare.

The clinical picture of perforative peritonitis exhibits an acute onset with intense stab-like abdominal pain usually primarily at the site of the lesion but soon generalized, with general abdominal rigidity and hypersensitiveness to pressure, vomiting, constipation and marked symptoms of shock. This is followed by a period of reaction with a lull in the abdominal symptoms and partial improvement in the general condition. The stage of diffuse peritonitis then rapidly develops or evidences of a circumscribed peritonitis may appear. The presence of peritonitis will usually be easily diagnosed and the history of onset will usually strongly suggest perforation. The presence of free gas in the peritoneal cavity is strong but not absolute evidence of the occurrence of perforation. The early appearance of tympanitic resonance over the abdomen and the obliteration of the area of hepatic dullness suggest free gas. In hospital cases when there is doubt the X ray may furnish conclusive evidence (F. H. Baetjer). The site of the perforation may be impossible to determine by examination of the patient. A careful history

of antecedent abdominal symptoms is perhaps the greatest single help. A right rectus incision will allow of exploration of the commoner sites of perforation. When the diagnosis of perforative peritonitis has been made the importance of early operation overshadows even that of a preoperative knowledge of the site of the initial lesion.

(c) *Biliary peritonitis* exhibits almost as manifold aspects as does appendiceal peritonitis. Mild subacute peritonitis expressing itself in adhesions between the gall bladder and surrounding structures is exceedingly common, especially in cases in which gallstones are present. As compared with appendicitis, cholecystitis shows a lesser tendency to result in spreading peritonitis without perforation. This may be due to the less frequent presence of virulent organisms in the gall bladder (bile does not favor the growth of cocci) or to the greater resistance of the wall of the gall bladder. Hugel has suggested that this greater resistance may be accounted for by the lesser vulnerability of the vascular supply of the gall bladder due to free anastomosis through its peritoneal attachment to the liver. A diffuse peritonitis may arise from cholecystitis without perforation however and may terminate fatally as the cases reported by Tripier and Paviot attest. Perforation of the gall bladder is due in some instances more to mechanical pressure on the wall from an impacted stone than to any pathological change due to bacteria. In other cases in which gallstones are present a virulent infection may be superadded with consequent ulceration and perforation. In still other cases an acute purulent cholecystitis without cholelithiasis may lead to perforation by ulceration or gangrene of the wall of the gall bladder. The type of peritonitis consequent upon perforation will depend upon the presence or absence of previously formed adhesions and upon the virulence of the organisms in the extravasated biliary contents. The anatomical situation of the gall bladder is favorable to circumscription of the process.

The symptomatology of the mild type of pericholecystic peritonitis is inextricably combined with that of cholecystitis and of gallstone colic. This mild peritoneal reaction may develop insidiously with no more clinical evidence than vague digestive disturbances, epigastric discomfort, tenderness in the region of the gall bladder and slight rigidity of the upper segments of the right rectus muscle. In an acute gallstone colic or in an acute flareup of a chronic cholecystitis it is largely a matter of interpretation how many of the symptoms and signs are to be attributed to peritoneal reaction and how many to processes within the biliary tract. Operation in or near the time of an initial acute attack may or may not show the presence of pericholecystic peritonitis with adhesion. In old cases however such evidences of peritoneal participation in the infective process are to be expected.

Perforation is not infrequently missed when it occurs in the midst of an attack of gallstone colic or of a recurrence of cholecystitis. One is too apt to forget that no matter how many previous attacks the patient may have weathered safely the danger of perforation still exists. Perforation of the gall bladder is not usually accompanied by as severe pain and shock as duodenal perforation. Where severe pain existed before perforation due to distention of the gall bladder the first sensation may be that of relief. The rapid recurrence of severe pain of a more diffuse nature and of a different character combined with generalized rigidity, diffuse sensitiveness, vomiting, constipation and evidences of shock (fall in temperature, rapid pulse) make the diagnosis of peritonitis evident.

(d) *Gonococcus Peritonitis*.—Peritonitis due to the gonococcus is clinically one of the most clearly defined types of peritonitis in that in the overwhelming majority of cases it occurs in women during the period of menstrual life, has as its point of origin an infected fallopian tube, exhibits a stormy onset but rarely fails to eventuate as a circumscribed pelvic peritonitis.

The salpingitis which gives rise by extension through the tube wall to gonococcus peritonitis is itself a secondary focus of the disease which begins as a rule with a vaginitis. The tendency of the gonococcus to penetrate the wall of the tube and set up a perisalpingitis varies markedly in different cases. The inflammatory reaction results in a marked thickening of the wall of the tube and as the peritoneal surface becomes involved it shows engorgement of its capillaries and fibrinous exudate. Adjacent peritoneal surfaces become infected by contact with the exudate on the tube. It is characteristic of this type of infection to spread not only to the peritoneal surface of contiguous structures but to penetrate into the subserous and muscular layers with the production of a marked inflammatory edema. The result of this tendency is the agglomeration about the infected tube of a mass of adherent coils of intestine. Very little free exudate may be present and the bulk and firmness of this inflammatory tumor is due largely to the thickening by intramural exudate of the walls of the loops of gut involved. This circumscribed form of peritonitis may of course result in abscess formation. In the majority of cases, if treated by rest during the acute period, it will regress leaving only a variable amount of fibrous adhesions. It is surprising how large an inflammatory tumor may thus disappear in the course of a few weeks. This is perhaps the most striking characteristic of gonococcus peritonitis. There is a marked tendency in a number of cases to a chronic course interrupted by acute recrudescences. When abscess formation has occurred it may rupture into the rectum or vagina, less frequently into the general peritoneal cavity.

The onset of gonococcus peritonitis is usually acute with abdominal

pain chill and fever The abdominal symptoms are often diffuse at the onset but their maximum is readily localized in the lower abdomen and usually more on one side Spontaneous pain is often very severe it is increased by *defecation urination or vaginal examination* Sensitiveness to pressure may be generalized at first but is soon most prominent over the affected tube Rigidity likewise is often diffuse in the period of onset but subsides quickly there remains rigidity of the lower segments of the recti muscles Vomiting is less frequent at the onset than in other types of peritonitis Constipation is usually present in the early stages There is as a rule *very little evidence of shock in spite of the acute onset* The pulse remains of good quality though increased in rate The fever is usually a marked feature of the onset often remaining at 103 to 105°F for the first few days after which it gradually subsides

Pelvic examination yields the most distinctive findings in gonococcus peritonitis Aside from the evidences of gonorrhea (Bartholinitis vaginitis *cervicitis urethritis) and possibly the demonstration of the organism in* smears or cultures the finding of a pelvic mass is a common accompaniment of gonorrheal perisalpingitis In the first day or two only a thickened sensitive tube may be felt combined with a vague resistance lateral to the uterus As the inflammatory mass increases it can be readily felt laterally and bulging into the cul de sac The uterus becomes fixed quite early *In the event of abscess formation fluctuation* may be made out by vaginal and rectal touch

In the diagnosis of gonococcus peritonitis from most conditions which simulate it (low lying inflamed appendix ruptured ectopic pregnancy twisted ovarian cyst abscess in the broad ligament) the pelvic findings *combined with the abdominal and constitutional symptoms will be decisive* Pelvic peritonitis arising from the female internal genitalia but not due to the gonococcus is chiefly associated with puerperal and postabortive infections In such cases proof of the causative organism may be impossible and only by the type of clinical course can one suspect the nature of the *infection*

Diffuse gonoccus peritonitis is one of the rarer diseases of the abdomen It may follow a simple gonococcal salpingitis or the rupture of an abcess Many cases reported have occurred in children Gonococci have been demonstrated in the exudate which is usually scanty The clinical course as a rule is characterized by an abrupt and stormy onset with chill abdominal pain *vomiting and distention The fever is high The course otherwise* is not appreciably different from that of diffuse peritonitis of other origin

(e) *Pneumococcus peritonitis* is among the rarer forms of peritoneal infection The comparatively scant mention it has received in the medical literature of the English speaking countries is quite striking when compared

to the attention French and German authors have devoted to its study

The pathogenesis of this form of peritonitis is still obscure and it is frequently classed as idiopathic It has been considered as a metastatic infection from foci of pneumococcus infection elsewhere in the body (lungs middle ear gall bladder) but clinical observation has not proved the pre existence of such foci in a preponderant number of cases A pneumococcus enteritis has been demonstrated in a few cases with evidence of extension through the gut wall (Flexner) The preponderance of females among the children affected has been coupled with the occasional demonstration of coincident pneumococcus salpingitis or metritis to support a theory that the female genitalia may constitute a portal of entry (Dudgeon and Sargent) In certain cases a pneumococcus bacteremia has been shown to be present in the early stages The balance of recent opinion favors the conception that such a bacteriemia is a feature of the onset of most acute pneumococcus infections the nasopharynx probably constituting the portal of entry Viewed in this light pneumococcus peritonitis may be considered as constituting simply one of the less usual secondary foci of development of the pneumococcus after its invasion of the blood stream

Children are far more frequently affected than adults and among the children affected those of the female sex greatly preponderate in numbers In one series of fifty two children under fifteen years of age forty five were females (cited by Hertzler)

The peritonitis caused by the pneumococcus is characterized by an abundant exudate of thick greenish yellow pus containing masses and strands of fibrin The commoner form is a circumscribed peritonitis of considerable extent occupying especially the lower abdomen The condition in its later stages really constitutes a large encysted peritoneal abscess and in children there is a tendency to spontaneous evacuation to the exterior at the umbilicus A less common form is a diffuse pneumococcus peritonitis in which the exudate is less abundant and fibrinous adhesions less of a feature

Pneumococcus peritonitis is characterized clinically by a very abrupt onset with severe diffuse abdominal pain and vomiting and a marked constitutional reaction (high fever rapid pulse leukocytosis) without usually much evidence of shock At this stage confusion with an acute perforative appendicitis is easy

The course after the onset is marked by a relative subsidence of the abdominal symptoms with continuance of severe constitutional disturbances indicating infection and toxemia (fever tachycardia headache delirium stupor) The occurrence of herpes has been signalized by a number of authors Distention appears after the first few days Tenderness and rigidity are diffuse but not marked features An initial diarrhea is some

times observed but the appearance of diarrhea after the first few days is common and rather characteristic of this type of peritonitis The constitutional symptoms of infection are often more prominent clinically than the abdominal symptoms Typhoid fever may be suspected At the end of a week or ten days there is often a rather sudden change for the better At about this same period signs of a localized purulent accumulation in the lower abdomen usually become evident (dullness in the flanks fluctuating mass edema of abdominal wall) Unless drainage by the surgeon is afforded the disease runs a subacute course with low fever toxemia emaciation diarrhea leading to a fatal issue During this subacute stage the disease may readily suggest tuberculous peritonitis

The clinical course of acute diffuse pneumococcus peritonitis which is perhaps the more common form in adults exhibits no features differing essentially from diffuse peritonitis due to other organisms The lack of a definite focus in the abdomen to explain the onset of a diffuse peritoneal infection should suggest the possibility of the pneumococcus as an etiological factor

(f) *Streptococcus Peritonitis*—The streptococcus is associated as the causative organism with certain severe forms of peritonitis and in particular with those developing from puerperal postabortive and postoperative infections There are likewise cases of streptococcus peritonitis in which the peritoneum constitutes a secondary focus by means of hematogenous metastasis from a primary streptococcus infection elsewhere in the body Such are the rare cases reported as occurring in erysipelas and the less uncommon type associated with streptococcus angina In the epidemics of septic sore throat in this country and elsewhere the occurrence of secondary streptococcic peritonitis was not an infrequent complication Such metastatic streptococcic peritonitis appears to occur more frequently in the female sex

In the hyperacute cases the pathological changes found in the peritoneal cavity at autopsy are minimal The disease kills by septicemia and toxemia before noteworthy changes have occurred The peritoneal surfaces affected are dusky red and show a fine granular deposit of fibrin A slight excess of brownish turbid peritoneal fluid is present The intestines are distended In the moderately acute cases a diffuse purulent peritonitis is found There is a paucity of fibrinous adhesions Rarely an encysted purulent peritonitis has been described

Clinically streptococcic peritonitis is characterized by the virulence of its course One to three days is the average duration Sudden onset chill headache diffuse abdominal pain vomiting and evidence of shock followed almost at once by the abdominal symptoms and signs of a diffuse peritonitis and by the constitutional evidence of an overwhelming infection

rapid collapse and death such is the picture of diffuse septic peritonitis due to the streptococcus

The Diagnosis of Peritonitis

The diagnosis of peritonitis in the diffuse stage is usually not difficult In the stage of onset the problem is less easy It is particularly in this early period that diagnosis is of value in furnishing therapeutic indications The most important help in the early diagnosis is that in every case of abdominal pain vomiting or disturbance of intestinal function the possibility of peritonitis should be considered and fully investigated (Ochsner)

Spontaneous pain sensitiveness to pressure muscular rigidity absence of abdominal breathing a facies expressing illness anxiety restlessness some elevation of rectal temperature a pulse relatively fast in proportion to the fever these are the cardinal symptoms of early peritonitis Nausea vomiting a dry tongue intestinal stasis are valuable confirmatory evidences The true facies abdominalis meteorism fecal vomit and dullness in the flanks are late phenomena The diagnosis should be made before they appear No one of the above symptoms is pathognomonic and not one is absolutely constant It is upon their association that the diagnosis must be made

The preexisting disease may markedly alter the picture of onset of peritonitis and so lead to the early symptoms being missed or misinterpreted This is especially true of the peritonitis arising in typhoid fever in pneumonia in far advanced carcinoma postoperatively and following abdominal contusions

In the differential diagnosis of peritonitis the most common conditions which may cause confusion are intestinal obstruction ruptured ectopic pregnancy gallstone and kidney colic acute gastroenteritis and pneumonia in children

Intestinal obstruction simulates peritonitis by sudden onset abdominal pain vomiting distention and evidences of constitutional shock The localized tenderness and rigidity, fever and leukocytosis of peritonitis are lacking however and there is a dissimilarity in the order in which the symptoms appear in the two conditions Distention is early in acute obstruction and its appearance is followed by the onset of vomiting in peritonitis the order is usually reversed Localized pain and tumor may be felt in intussusception but there is no true rigidity of the overlying abdominal wall In most cases of obstruction the pain is more paroxysmal and less constant than in peritonitis Intestinal patterns are a feature common in obstruction and rare in peritonitis In many cases of obstruction the constitutional symptoms of collapse are more gradual in development and

differ in character from the initial symptoms of shock with subsequent rally which characterize peritonitis

The sudden sharp abdominal pain due to rupture of a tubal pregnancy followed by rapidly increasing symptoms of collapse and accompanied by evidences of peritoneal irritation due to the effusion of blood into the peritoneal cavity may simulate the onset of an acute peritonitis The resemblance may be heightened by the occurrence of initial vomiting and of some leucocytosis The very rapid appearance of serious collapse the blanched mucous membranes fading pulse restlessness and thirst should at once suggest hemorrhage The absence of fever the lack of abdominal rigidity the early appearance of dullness in the flanks the finding by pelvic examination of a soft cervix and possibly of a mass laterally a history often of diminished flow or a missed period should prevent any serious confusion with peritonitis at the onset After the first few days an infected hemoperitoneum may lead to a true peritonitis

Renal colic has been mistaken for peritonitis and more particularly for periappendiceal peritonitis When the pain of renal colic is chiefly in the lumbar and lateral region of the abdomen and accompanied by the characteristic reflection downward to the testicle by vesical tenesmus *oliguria and perhaps hematuria and pyuria such an error* will *rarely occur* In some cases however gastrointestinal symptoms (vomiting tympany constipation and muscular rigidity) predominate (Sternburg) In such cases the history of previous attacks of colic dysuria the examination of the urine the lack of fever and leukocytosis and careful determination of the site and reflection of the pain should suggest the possibility of renal or ureteral colic

Gallstone colic may likewise be mistaken for peritonitis Such an error is less serious than that not infrequently made of assuming that biliary perforation in cholecystitis is merely another attack of gallstone colic

Acute gastroenteritis not infrequently suggests peritonitis by the presence of diffuse abdominal pain vomiting distention and fever The history of the onset will usually show that a period of general malaise headache and often fever preceded by some hours the appearance of the gastro intestinal symptoms Of these latter vomiting is usually the first to appear Distention appears early in many cases The abdominal pain is diffuse and colicky General tenderness without rigidity is the rule The pulse is not fast in proportion to the fever Leukocytosis is absent or slight The early appearance of diarrhea is common

Pneumonia especially in children may give rise to abdominal pain and *rigidity vomiting constipation and fever at a* stage when few physical signs can yet be found over the lungs The lack of deep tenderness in the abdomen the relaxation of the abdominal wall at some stage of respiration

the marked early elevation of the temperature and leukocyte count the absence usually of a disproportionately rapid pulse the polypnea expiratory grunt cough herpes and flushed face should suggest the pulmonary origin of the symptoms

Less frequent causes of confusion because of their relative rarity are acute hemorrhagic pancreatitis gastric crises of tabes lead colic Dietl's crises acute torsion of a pedunculated ovarian cyst acute pericarditis in children Henoch's purpura acute suprarenalitis The symptomatology of these conditions cannot be reviewed in sufficient detail in this section to aid materially in the often extremely difficult task of their differentiation from acute peritoneal infection In all cases of peritonitis exhibiting atypical features the possibility of the presence of any one of these conditions must be investigated

The Treatment of Acute Peritonitis

There does not exist any longer a medical treatment of peritonitis to be considered as an alternative to surgical measures, but in this as in all other surgical diseases operation constitutes only a portion of the therapy required The prophylaxis of peritonitis the preoperative care the indications for operation postoperative treatment of the patient with peritoneal infection are subjects of concern to all physicians

The prophylaxis of peritonitis consists essentially in the prevention or the early recognition and treatment of the lesions most likely to be complicated by peritonitis The prevention of typhoid fever by typhoid vaccination and by sanitation is the best prophylaxis of typhoid perforation and peritonitis The thorough treatment by medical or if necessary surgical means of gastric and duodenal ulcers will reduce the frequency of perforations from this source The early recognition of appendicitis will allow of appendectomy before the infection has obtained an independent footing in the peritoneum Obstetrical asepsis will eliminate the dreaded puerperal peritonitis One of the most important results to be hoped for as a result of the campaigns against venereal disease is the reduction in the number of cases of gonococcic peritonitis in women The correct diagnosis of intestinal obstruction will allow of its surgical relief before it has led to peritonitis An appreciation of the role played by gallstones in the pathogenesis of biliary peritonitis with or without perforation will influence the physician in his decision as to the advisability of cholecystectomy in such cases

The preoperative treatment of peritonitis may be briefly summed up as an avoidance of purgatives the postponement of narcotics until the decision as to operation is made rest and starvation The dangers of purgation in any case of abdominal discomfort before a diagnosis has been made cannot be too strongly insisted upon It is perhaps the commonest

serious mistake in medical practice When peritonitis is suspected the therapeutic aim should be to keep the intestines at rest to favor localization of the process For this reason not only are all purgatives barred but food is withheld and the patient kept absolutely quiet in bed Ice bags to the abdomen are used The patient is best placed in a semi sitting position If nausea and vomiting are prominent symptoms gastric lavage should be employed A continuous rectal infusion of normal saline will supply the necessary fluid to the body Very severe pain may be met by small doses of morphia but until the diagnosis and decision as to operation have been made great care should be taken to avoid masking the symptoms by the use of narcotics

Indications for Operation —Surgical interference in peritonitis aims at (a) removal of the causative lesion (b) drainage Both are attempts to assist nature at the point at which her natural defenses are the weakest at the moment of operation (*e g* at the site of the causative lesion or at the site of a well localized purulent accumulation) If the most active focus of infection is eradicated or by means of drainage to the exterior is prevented from further diffusion nature will be better enabled to overcome the infection in regions in which it has gained a less firm footing At any rate the natural defensive measures of the body are more likely to be successful in this task than are extensive surgical procedures with multiple drainage incisions washing out of the peritoneal cavity attempts at mechanical cleaning or sterilization etc

When considered in relation to the question of the advisability of operation cases of peritonitis fall into two primary categories those in which we know the primary focus of disease and those in which we do not

In cases in which the point of origin of the peritonitis is not known and in which no well localized focus of infection is evident operation should be judged as an exploratory procedure If it fails to afford an opportunity to attack the causative lesion or some other well localized focus it is unlikely to be of great benefit from any other aspect On the other hand it may gravely impair the general resistance of the patient or may disseminate infection previously relatively localized

An exploratory operation of this sort is most likely to be successful and least likely to be harmful if undertaken very early when the peritonitis is still localized so that search of the abdominal cavity is less likely to spread infectious material Early in an infection which exhibits signs of virulence it may be safer to operate and search for the cause than it is to wait in the hope of enlightenment and so allow the process to become diffuse

When the case is first seen as a rapidly spreading or diffuse peritonitis without any evidence of the focus of origin it is usually safer to wait the chance of secondary circumscription of the process rather than to add the

shock of an operation of dubious utility at this stage to those forces already threatening to overwhelm the patient

When a diagnosis of the causative lesion has been made the nature of this lesion will play a part in the decision as to operation along with the extent of the peritonitis and the condition of the patient

A diagnosis of perforation or of intestinal obstruction is an indication for immediate operation irrespective of the extent of the peritonitis provided the condition of the patient permits The period of intense shock at the onset of certain perforations is considered by some surgeons a less favorable moment than a few hours later when the patient begins to react No hard and fast rule of this sort should be drawn however and the danger of delay should be constantly in mind in judging the situation in each individual case Of course when the patient is *already moribund when first seen* most surgeons will hesitate to interfere

An appendicular peritonitis when still localized constitutes an indication for immediate operation but when rapidly spreading with the patient showing evidences of severe intoxication it is sometimes wiser to trust to non surgical measures to assist the tendency of such lesions to a secondary circumscription which will offer a more favorable opportunity for successful operation A circumscribed periappendiceal peritonitis does not demand immediate operation if there is evidence of subsidence of the infection but if indications of pus formation exist operation is indicated

The tendency of acute cholecystitis to produce only a localized peritoneal reaction leads many men to adopt a policy of watchful waiting in such cases This is more justifiable in cases in which the history warrants the supposition that the gall bladder is imbedded in adhesions than where no evidences of previous attacks exist In the presence of the widespread peritonitis of cholecystic origin it is often wiser to await a secondary circumscription of the process than to operate in the stage of acute spreading infection Acute gonorrheal pelvic peritonitis contraindicates operation as experience has shown that such lesions are far more apt to generalize after operation than without it All circumscribed peritoneal abscesses whatever may be their origin indicate operation for their relief

The Postoperative Treatment of Peritonitis —The chief indications in the postoperative care of peritonitis are to secure rest for the patient, to employ suitable supportive measures to furnish sufficient nutrients and fluids and to combat complications

A semi sitting position will not only afford the patient a maximum of rest, but also favors drainage of the exudate towards the lower abdomen whence it is least readily absorbed This position is maintained by the use of a comfortable back rest a pillow firmly lashed across the bed to hold up

the buttocks and a foot rest Upon skillful adjustment of these supports depends the comfort of the patient

When pain or restlessness are marked morphia is indicated Small doses gr 1/8 to gr 1/6 (7 to 10 mgm) are usually sufficient to blunt the pain and will not harmfully limit intestinal peristalsis if repeated at ten hour intervals when necessary

Of the supportive measures the most important is to furnish sufficient fluid As this cannot be done by ingestion without exciting too much activity in the small intestines the use of rectal infusions has become universal Continuous rectal infusion of normal saline solution or of tap water by the Murphy drip method is the most efficient method One pint an hour may be given at first by this method but after the first few hours it is wisest to reduce the flow to one half of this amount At least three quarts should be given if possible

When collapse is marked the rectal infusion alone may not furnish fluid rapidly enough to keep up the pressure in the atonic circulatory system In such cases saline solution intravenously should be employed Care should be taken to control the inflow of fluid so as to diminish the strain on the heart muscle produced by too rapid increase in the blood volume The transfusion of a liter of saline solution should occupy at least forty minutes and not more than this amount should be given at one time Citrated whole blood deserves a trial in place of simple saline solution in case of postoperative shock

Heat is likewise an important supportive measure and the greatest attention should be paid to the proper covering of the patient while he is coming out from under the ether and thereafter the bed to which he is brought should be thoroughly warmed by hot water bottles and these should be packed about the patient care being taken to avoid accidental burns The use of a flat electric pad will be found a convenient means of applying heat to the abdomen

When the patient s condition demands a more rapidly acting form of stimulant than the plain saline infusion adrenalin may be given Fifteen minims (1 c c) of adrenalin (1 1 000 solution) may be added to the liter of normal saline solution Camphorated oil 2 c c and caffein sodium benzoate gr 3 (0 2 gm) are also useful stimulants They are best administered intramuscularly

A little crushed ice may be given the patient by mouth if thirst is troublesome but beyond this no fluid or food should be taken until the passage of flatus indicates that peristalsis is being resumed Small amounts of liquids (milk or albumin water oz 3 100 c c) may then be allowed at intervals of four hours and may be followed the next day by an easily digestible soft diet (junket arrow root custard etc) If the f ting period

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pathogenesis and the clinical forms of this malady The present status of the subject nevertheless leaves us with many important que tions still unsettled

Etiology

The tuberculous nature of the dise se is demonstrated not only by the gro s and histological picture of the inflammatory tissue but by the demon tration of the tubercle bacillus T e tubercle bacillu is not usually demon trable in the exud ite by staining methods and it can be found in ti sue sections in but little more than half of the cases Animal inoculations (guinea pigs) with the exudate yield a positive result in about fifty per cent of the cases Inoculation of tissue emulsions are however uniformly positive (Borchgrevink) The frequency of occurrence of peritoneal tuber culo is is difficult to determine Bircher reports finding its presence in 3 5 per cent of over 19 000 autops s collected from the literature Caird in 6 366 surgical patients found only 0 5 per cent in whom this diagno is had been made The statistics on the frequency of its occurrence among fatal cases of tuberculosis indicate its pres nce in about ten per cent of such cases Schlimpert considers tuberculous peritonitis as the third most frequent localization of tuberculosis in the human body

Tuberculous peritonitis is most commonly seen in adolescence and early adult life Cases in children under two years of age are decidedly rare and after forty the incidence again dim rishes markedly Advanced age is how ever by no means incompatible with this type of tuberculous infection

The disease in children before puberty attacks both sexes equally After this period the greater number of cases are seen in women Statistics bearing on this point are unsatisfactory because based for the most part on autopsy cases or on the experience of gynecological clinics

It is traditional to ascribe to alcoholism and to cirrhos s of the liver a place as predisposing factors in the etiology of tuberculous peritonitis The observations on which this relationship has been founded we owe for the most part to French clinicians Thi associ ition appea s to be less usual in this country Traumatism has appea ed in some cases to be a f ictor in the localization or in the dissemination of a tuberculous infection of the pe i toneum

Pathogenesis

Peritone il tuberculosis is almost always accompanied by demonstrable tuberculous lesions elsewhere in the body The lesions most commonly found associated with it are tuberculosis of the lungs of the lymph glands of the genital organs and of the bones In mo t cases the clinical hi tory or the pathological examination indicates that the infection of the peritoneum

must exceed forty eight hours nutrient enemata should be given A five per cent glucose solution is more likely to be absorbed and is less irritating to the rectum than the nutrient enemas containing egg whiskey etc that have been employed in the past As large an amount of the glucose solution should be given as is tolerated without expulsion of the fluid

Postanesthetic vomiting is best relieved by washing out the stomach with a quart or more of sodium bicarbonate solution (four per cent) If vomiting is at all marked after the first six hours this procedure should not be delayed and should be repeated if necessary A Rehfuss tube may be employed and may be left in situ if a repetition of the lavage seems probable

Distention may be relieved by the passage of a rectal tube Turpentine stupes are occasionally of value also Pituitrin (1 c c hypodermically) may give relief and eserin sulphate (gr 1 1/100 0 6 mgm) is likewise sometimes of benefit after the first two days Asafetida enema may be given a trial

When the free passage of flatus indicates the resumption of peristalsis the bowels may be cleared by giving a moderate dose of castor oil or of magnesium sulphate

During the convalescence from peritonitis measures should be employed to build up the patient s weight and strength General massage is valuable and after the first month abdominal massage may be cautiously essayed The resumption of activity should be very gradual A full diet should be slowly arrived at The frequently present tendency to constipation should be combated by the inclusion of an increased amount of fruits and vegetables in the diet One ounce of mineral oil night and morning will usually be found helpful Out of door life is the best tonic

Tuberculous Peritonitis

The present conception of tuberculous peritonitis has been arrived at through the collected observations of a long series of medical investigators Early in the nineteenth century the memorable work of Bichat on the diseases of serous membranes first established the occurrence of chronic inflammatory processes of the peritoneum Some years later Louis as a result of his studies on the pathology of tuberculosis was able to demonstrate the tuberculous nature of certain types of such chronic inflammations His conclusions were firmly established by the support of many other pathologists and clinicians of his day Koch s discovery of the tubercle bacillus and the opening of the era of abdominal surgery in the latter half of the century led to a vastly increased amount of knowledge concerning the

in an attempt to keep the lesion hemmed in. Adjacent enlarging tubercles fuse by juncture of their caseous centers and so macroscopic tubercles and tuberculous nodules are formed. These large lesions may break down by puriform softening and so form abscesses and ulcerations of the body structures in which they are situated.

The proportion between the amounts of caseous material and of connective tissue encapsulation in these tuberculous lesions is strikingly variable. This variability determines two of the main clinical and pathological types the caseous (and ulcerative) and the fibrous. In the one type of infection characteristic large caseous or puriform masses are seen encapsulated by connective tissue while in the second type there is seen the development of a great matrix of fibrous tissue in which are to be found small caseous foci.

In the gross pathology of tuberculous peritonitis the picture varies according to the stage in which the case is seen according to the type of invasion of the peritoneum which has occurred and according to the sequence of events thereafter. The earliest stage is that of miliary tubercle on the peritoneal surface. If the process is generalized from the start these may develop over the whole of the visceral and parietal layers being however more numerous as a rule in the sheltered recesses afforded by the subdiaphragmatic spaces the region of the cecum and the pelvis. If the invasion of the peritoneum has been secondary to a focus of intraabdominal tuberculosis the miliary tubercles on the serous membrane will usually at first be confined to the vicinity of this focus. In either case healing and replacement by scar tissue of these early lesions may occur or they may develop into caseous nodules or masses enveloped in fibrous tissue which mats together all the abdominal viscera or a mixed picture may develop with healed lesions caseous and fibrous masses and fresh crops of miliary tubercles all present at the same time at different points in the peritoneal cavity.

The formation of peritoneal exudate is apparently due to irritant substances diffused from the tuberculous tissue. It is more marked in the presence of actively progressing lesions than when encapsulation by fibrous tissue is a marked feature of the process. In the later stages the resorptive power of the peritoneum is probably much impaired so that such exudate as is formed tends to remain in the peritoneal cavity. Certain cases show a tendency from the start to be accompanied by marked effusion even though the character and extent of the tuberculous lesions offer no ready explanation why this should be the case. This group is clinically and pathologically sufficiently distinct to be designated as the ascitic form of the disease. The exudate in tuberculous peritonitis is usually serous (or serosanguineous in the early cases) light greenish yellow in color clear or opalescent. It

constitutes a secondary localization of the disease resulting from dissemination from these older foci There is little evidence that the tubercle bacillus entering the body by inhalation or ingestion ever determines a peritoneal tuberculosis as a primary focus

The secondary invasion of the peritoneal cavity by the tubercle bacilli derived from foci situated extraperitoneally may result from simple extension of the focus through tissues or lymphatic channels or by means of the blood stream

In the first instance a localized peritonitis is the early and often the sole result In the second type of case a diffuse peritoneal tuberculosis appears at the onset The localized tuberculous peritonitides frequently seen about a tuberculous fallopian tube or a tuberculous cecum or about tuberculous caseating mesenteric glands are examples of invasion of the peritoneum by extension of a tuberculous focus Of course such localized tuberculous peritonitis may in many instances not remain circumscribed On the other hand the type of generalized tuberculous peritonitis without evidence of a primary focus of intraabdominal tuberculosis must be taken to represent an invasion of the peritoneum through hematogenous channels The occurrence of this type of peritoneal tuberculosis as a part of a general miliary tuberculosis supports this point of view

The simultaneous tuberculous infection of one or both pleural cavities together with the peritoneum lends some color to the theory that in some instances the strain of bacillus involved has a predilection for serous surfaces

General Pathology

The key to the multiplicity of forms assumed by tuberculous peritonitis lies in an analysis of the steps in the production of the three main gross features of its pathology These are the specific tuberculous lesions the exudate and the fibrinous adhesions

The tuberculous lesions in tuberculous peritonitis are constituted by the pathological tissue formed in the structures invaded in the attempt to encapsulate the tubercle bacilli The earliest stage is the microscopic tubercle an agglomeration of lymphocytes and giant cells surrounding and imbedding the tubercle bacilli The development of connective tissue at the periphery and the occurrence of caseation at the center of the tubercle is the next step in its growth If the lesion is arrested at this stage the caseous center will either be invaded by connective tissue and so eventually replaced by scar tissue or if too large for such organization it will remain as a firmly encapsulated caseous or calcareous mass If however the tubercle enlarges it is by spread of the central caseation and by the starting up of fresh tubercles in the zone of connective tissue The latter is constantly expanded

cardia cyanosis) mask the onset of the peritoneal involvement which may o'y become apparent when the abdominal distention grows marked In other instances symptoms due to involvement of the lungs the pleural cavities etc may overshadow those caused by the peritoneal lesions In some cases however an acute abdominal syndrome appears Generalized bdominal pain is complained of nausea and vomiting occur gaseous distention constipation or diarrhea may be present Fluid rapidly becomes evident at first in the flanks and later distending the entire abdomen In such cases the disease is usually rapidly fatal

When an acute miliary involvement of the peritoneum occurs as a result of sudden extension of a localized focus of intraabdominal tuberculosis (tuberculous fallopian tube mesenteric gland etc) the resulting pathological picture varies from that above described only in the accentuation of the peritoneal involvement in the region of the primary focus Clinically certain of these cases are characterized by the occurrence after a period of more or less well defined symptoms due to the original focus of acute abdominal and constitutional symptoms In certain instances the resemblance to typhoid fever may be misleading (Osler) In others the predominance of the abdominal symptoms may suggest an acute non tuberculous peritonitis Owing to the lesser extent of the tuberculosis outside of the peritoneal cavity these cases run a longer course than those included in the category of general miliary tuberculosis Usually there is an evolution of the lesions toward the caseous form The fluid exudate diminishes in amount Plastic masses of adherent and thickened intestines become palpable The clinical course becomes subacute or chronic with remittent fever sweats and emaciation

A subdivision of the form just described is constituted by those cases in which the primary focus of intraabdominal tuberculosis gives rise by sudden extension to an acute localized peritonitis The pathological findings in such cases are limited to the area about the original focus The peritoneum in the immediate vicinity is thickly studded with tubercles and a beginning walling off process by fibrinous adhesions and omentum is found These cases are often clinically indistinguishable from acute non tuberculous inflammations in the same regions and most of them that have been recorded have been seen at operation due to this mistake in diagnosis The differentiation between acute tuberculous peritonitis in the ileocecal region and acute appendicitis has proved especially confusing

Chronic Forms of Peritoneal Tuberculosis

Ascitic Form —Ascites is a feature of almost all forms of tuberculous peritonitis at some stage of the disease Its presence is usually coincident

contains a very variable amount of fibrin The specific gravity is usually between 1 018 and 1 026 The exudate in the advanced cases of the caseous and fibrous types is sometimes purulent even in the absence of mixed infection

The fibrin in the exudate is deposited on the peritoneal surfaces and leads to their agglutination The extent to which this occurs varies greatly The smaller exudates frequently contain the most fibrin These fibrinous adhesions serve as frameworks for the ingrowth of connective tissue In cases in which this fibrotic tendency is marked the parietal peritoneum becomes greatly thickened the viscera are sheathed in sclerotic tissue and welded together in a mass adherent to the abdominal walls and to each other In this matrix of connective tissue are to be found caseous areas which denote the tuberculous nature of the fibrosis which has followed the early non specific fibrinous adhesions

Clinical and Anatomical Types of Tuberculous Peritonitis

Certain clinical and pathological types of tuberculous peritonitis tend to be fairly constantly reproduced in the experience of all observers The variations between them are dependent upon differences in the mode of origin of the peritoneal infection in the degree of rapidity of evolution of the disease and in the predominant type of tuberculous lesion produced

Acute Forms of Peritoneal Tuberculosis

While in general running a chronic course peritoneal tuberculosis may be characterized in some instances by an abrupt onset This is the case where a diffuse or localized infection of the peritoneum has occurred suddenly with dissemination of tubercles over the whole or a part of the serous membrane

The peritoneum is frequently involved in generalized miliary tuberculosis In such instance the visceral and parietal layers of the peritoneum are more or less thickly studded by miliary tubercles Their gross appearance is that of fine seeds of a grayish or yellowish semi translucent color and of firm consistency They are arranged irregularly along the course of the finer blood vessels They are apt to be more numerous in the omentum and in the region of the liver the spleen the cecum and the pelvic organs The peritoneal membrane loses its luster and exhibits varying degrees of congestion and subendothelial ecchymosis The abdominal cavity usually contains a considerable peritoneal exudate of light greenish yellow fluid which in hyperacute cases may be blood tinged The fibrin content is slight and fibrinous adhesions are not a marked feature

The corresponding clinical picture is very variable In certain cases the marked constitutional symptoms (fever asthenia rigors sweats tachy

diffuse or localized miliary tuberculosis of the peritoneum In many cases however the stage of miliary lesions is clinically practically absent and the symptomatic picture dates essentially from a time when caseous and ulcerative lesions are present

In generalized peritoneal tuberculosis of this type the peritoneal membrane is greatly thickened by tuberculous infiltration with the formation of large caseous nodules and by the deposition of fibrin on the surface The small intestines are matted together and bound down by bands of fibrous tissue which fuse together the thickened and distorted coils The mesentery is thickened leathery retracted and contains large caseous glands *The omentum thoroughly infiltrated and seeded with tubercles* is usually rolled up into a cord like mass lying across the upper abdomen The recesses of the peritoneal cavity are filled by masses of caseous and necrotic material The parietal peritoneum is everywhere adherent to the viscera In such pockets as remain collections of puriform material or of seropurulent exudate are found In less extensive cases the process *may be advanced to this stage only in a portion of the peritoneal cavity* as for instance in the pelvis to which it may be confined by massive fibrous adhesions

Of these localized types that which affects the region of the cecum is an important and not infrequent one The subdiaphragmatic spaces and the sigmoid region are also occasionally the sites of similar processes

Clinically there may be a first stage constituted by the symptoms accompanying an acute diffuse tuberculosis of the peritoneum or by those associated with the chronic ascitic form of the disease Where the primary stage is latent the onset is usually gradual with loss of flesh and appetite evening elevation of temperature (99° 101 F) night sweats chills and tachycardia *Gastrointestinal symptoms appear early* Colicky abdominal pain and constant vague discomfort occasional nausea or vomiting a marked tendency to meteorism and alternations of obstinate constipation with diarrhea are frequent

Referred pains are often felt in the back and down the thighs Painful *urination is* not an infrequent symptom especially in women The abdomen enlarges and this distention due in part to walled up exudate and in part to gaseous accumulations is frequently asymmetrical Percussion may reveal corresponding areas of dullness and of tympany There is usually no marked sensitiveness to touch On deep palpation irregular rounded masses sometimes putty like and sometimes firm in consistency may be felt A transverse mass across the *upper abdomen* can be palpated corresponding to the thickened omentum and transverse colon These tumors are usually immovable they may yield a sensation of crepitation and gurgling On rectal palpation the rectovesical pouch is found filled with an

with the rapid growth of young tubercles on the peritoneal membrane It is most common therefore in the early stages or accompanying flare up in chronic processes due to a fresh extension of the disease In certain cases however it is from the start the most prominent expression of the disease both clinically and pathologically This so called ascitic form of peritonitis was long recognized as a clinical entity even before its tuberculous nature was prove Pathologically these cases show an abundant serous exudate usually lemon or straw colored less frequently sanguinolent rarely yielding tubercle bacilli on microscopic examination but occasionally giving positive results through animal inoculation Its fibrin content is low and there is very little deposition of fibrin upon the peritoneal membrane The latter is usually relatively normal in appearance though careful search discloses scattered tubercles of varying sizes Many of these when seen may be in process of regression (fibrosis calcification)

Clinically such cases are characterized by the insidious development of painless ascites Constitutional effects are relatively mild though asthenia malnutrition a slight evening elevation of temperature and vague digestive disturbances (anorexia gaseous distention twinges of abdominal pain constipation) are frequently noted at the onset The abdomen on examination is found to be uniformly distended the superficial abdominal veins while frequently visible because of loss of subcutaneous fat are rarely enlarged There is shifting dullness in the flanks A fluctuation wave may be made out Tenderness on pressure is variable and usually not marked

The disease runs a chronic remittent course the ascites for many months lessening and recurring often with considerable rapidity The degree of distention occasionally necessitates paracentesis Recovery occurs in the majority of cases Occasionally there is a gradual transformation to a well marked fibrous type of the disease less frequently a rapid development of caseous and ulcerative lesions terminates the patient s life

This form of tuberculous peritonitis is most common in children especially girls about the age of puberty (ascite essentielle des jeunes filles) In adults the onset of tuberculous peritonitis may be characterized by a similar ascites but this is usually a relatively brief phase in the development of the disease The fluid usually disappears wholly or in part and the symptoms and signs of the caseous or of the fibrous type become evident

Caseous and Ulcerative Form —From the point of view of the pathological lesions the caseous and ulcerative form of tuberculous peritonitis is a late stage of the disease produced by development from the primitive miliary tubercle From the clinical point of view as well in certain cases it constitutes a secondary phase sequential to an original clinical picture of

bronzing On palpation the tumors formed by the matted intestinal coils are readily felt Vaginal and rectal examination shows marked fixation of the pelvic viscera and a firm mass in the cul de sac

Intestinal obstruction is the commonest complication in this form of the disease As it is usually due to retraction of the fibrous tissue its onset is frequently gradual The early stages are often characterized by colicky pain coming on at a fairly definite interval after eating The height of each paroxysm coincides with gaseous and liquid gurgling noises loudest over the site of the obstruction and indicating the forcing of the intestinal contents through the constriction By careful observation of these phenomena an accurate localization of the obstruction can sometimes be made in these emaciated cases Sudden complete obstruction is however not infrequent and may occur when the disease is apparently cured Occasionally it initiates the clinical picture

Mixed Form—While the majority of cases of tuberculous peritonitis can be classified under one or the other of the above described forms the occurrence of mixed forms is shown by autopsy and operation to be very common The mixture of acute lesions with those of a more chronic type is frequent in cases which have been carried off by a sudden flare up or extension of the disease Caseous lesions may appear in one area of the abdomen while a predominantly fibrous process is found elsewhere The fibrous form may be accompanied by marked ascites Caution is always advisable in predicting the pathological findings

Diagnosis of Tuberculous Peritonitis

There is frequently serious difficulty in making a positive diagnosis in tuberculous peritonitis This difficulty is due not only to the occasional latency of the disease but also the fact that the history symptoms physical examination and special tests rarely yield pathognomonic data Moreover the outstanding clinical features of tuberculous peritonitis fever abdominal discomfort digestive disturbances ascites palpable tumors are each common to a number of other pathological conditions After the most careful consideration of the differential data the physician is usually driven to making a diagnosis based on his estimate of the balance of probabilities The special problems of analysis cover a wide range and since they vary greatly according to the stage of the disease they are best considered grouped in accordance with that principle

In the acute forms of tuberculous peritonitis the constitutional symptoms are frequently most marked and the general clinical picture may suggest typhoid fever (fever headache malaise vague gastrointestinal symptoms) The evidence of tuberculosis elsewhere in the body the appearance

irregularly rounded doughy mass in which firmer nodules can sometimes be made out

This form of the disease usually runs a fatal course by progressive wasting or as a result of complications Of these latter the setting up of tuberculous foci elsewhere in the body meninges lung the occurrence of generalized miliary tuberculosis and certain intraabdominal complications are the most usual The intraabdominal complications usually seen are due to the ulcerative effects produced by the puriform softening and liquefaction of caseous tuberculous lesions in the walls of the intestines and other viscera By this means fecal fistulae are formed between adjacent loops of gut or through the abdominal wall at the umbilicus The result in either case is secondary infection of the peritoneal cavity with rapid death by sepsis In rare instances the disease gradually goes over into a fibroid and less active form and may progress to a relative healing

The Fibrous Form —In this form the production of connective tissue is the predominant type of reaction to the tubercle bacilli As this is essentially a healing process this form clinically is often milder and more chronic than those previously described It is a late stage of the disease in the pathological sense but from the clinical point of view the earlier stages are frequently asymptomatic and the patient comes to the physician first presenting the clinical picture of the fibrous form It may likewise however develop gradually after a preceding phase of ascites or of the caseous form of the disease

In the pathology of this form of tuberculous peritonitis an outstanding feature is the absence of exudate hence it is often spoken of as the dry form When it is generalized the peritoneal cavity is obliterated by the marked development of fibrous adhesions in broad sheets and bands which bind down the intestines and attach them to the posterior wall and to the viscera In this mass of connective tissue calcareous and caseous foci may be discovered marking the site of degenerated tubercles The intestines are distorted in their relations usually drawn toward the right side of the abdomen with some coils impacted and adherent in the pelvis Marked distention of certain loops may indicate the site of partial intestinal obstruction due to strangulation or obturation The capsules of the solid viscera are often greatly thickened and the peritoneal membrane itself is leathery and lusterless

This form of the disease is usually afebrile There is marked emaciation and weakness Digestive disturbances (anorexia colicky abdominal pain after eating borborygmus constipation) are present to a greater or lesser degree The accentuation of the abdominal pain on movement or stretching is characteristic of this form The abdomen is often retracted The skin shows in many cases a sallow color which sometimes amounts to a true

rub over the liver should be searched for after the fluid is withdrawn The fluid should be inoculated into a guinea pig

The abdominal tumors which develop in the caseous and in the fibroid forms of peritoneal tuberculosis frequently lead to the diagnosis of abdominal new growths and the reverse error is no less likely to occur Pelvic tuberculosis with loculated exudate in the lower abdomen may readily be mistaken for ovarian cyst The fibroid forms with partial intestinal obstruction strongly suggest carcinoma of the intestines The diffuse caseous forms may be taken for general carcinosis of the peritoneum The history of an earlier ascitic phase when obtainable is strong evidence of the tuberculous nature of the affection Fever and sweats point in the same direction Palpation of the rolled up infiltrated omentum lying athwart the abdomen when combined with the fairly characteristic putty like mass of adherent intestinal coils in the pelvis felt per rectum is very suggestive of tuberculosis The wooden hardness of carcinomatous masses is not found in the tuberculous lesions In general carcinomatosis of the peritoneum metastases may appear in the inguinal glands If these are enlarged one can readily be excised for diagnostic purposes The formation of a fecal fistula at the umbilicus is characteristic of tuberculous peritonitis

Aside from the analysis of clinical symptoms and physical findings recourse may be had to special diagnostic measures Of these exploratory laparotomy when indicated is of course the most certain though in some cases histological examination of the tissues or even animal inoculations may be further necessary In some instances a small incision in the mid line which can well be carried out under local anesthesia is all that is required

The examination of the physical and chemical characteristics of the exudate is never decisive A marked preponderance of lymphocytic cells is of some diagnostic value Courmont has presented evidence of the possession of higher agglutinating powers for tubercle bacilli by the exudate of tuberculous peritonitis than by the peritoneal fluid in other diseases showing ascites

Tubercle bacilli are rarely found in smears made from the centrifugalized sediment Inoculation into guinea pigs of the sediment gives positive results in fifty per cent of the cases If suspected pathological tissue is obtained for examination sections stained for tubercle bacilli should be made A portion of the tissue should be digested with antiformin and stained smears made A third portion should be emulsified and inoculated into several guinea pigs If the anterior abdominal wall is inoculated the inguinal glands will show tuberculous changes much sooner than is required to obtain dependable data following inoculation of the peritoneal cavity

of peritoneal effusion the relative tachycardia instead of bradycardia the absence of rose spots and of a palpable spleen will enable a clinical distinction to be made which will be confirmed by the absence of the typhoid bacillus from the blood urine and stools the negative Widal test the absence of leukopenia and occasionally by the discovery of the tubercle bacilli in the sputum in the peritoneal exudate or rarely in the blood

The acute generalized form of tuberculous peritonitis may occasionally simulate an acute diffuse peritonitis of the non tuberculous variety The onset of the tuberculous variety is rarely as sudden as that of perforation peritonitis and lacks the element of constitutional shock so prominent in this latter In the acute tuberculous form there is usually lacking any indication of an abdominal source of the peritoneal infection while in diffuse peritonitis due to other organisms a primary focus is more commonly found The greatest difficulty may arise in distinguishing between the later stages of pneumococcus peritonitis and acute tuberculous peritonitis The marked leukocytosis of the pneumococcal infection will usually be helpful in this respect but occasionally the blood count also may be misleading The fluid exudate is usually larger in amount in the tuberculous peritonitis and if puncture is done the physical and cultural characteristics of the fluid will be decisive

The acute localized forms of peritoneal tuberculosis frequently simulate acute purulent infections at the same sites (acute pelvic tuberculosis simulating gonococcal peritonitis acute ileocecal tuberculosis resembling appendicitis etc) The differential characteristics are not sufficiently reliable to warrant withholding operation when there is possible urgent need of it

The chronic ascitic form of tuberculous peritonitis is more common in children an age when ascites from other causes is relatively rare and when those cases which do occur are usually readily attributed to evident cardiac or renal lesions Rarely congenital syphilis of the liver may lead to ascites The enlarged liver and evidences of portal obstruction jaundice bile pigments in the urine other stigmata of syphilis and the Wassermann test will clear up the diagnosis In adults a more serious difficulty arises in differentiating the effusion due to peritoneal tuberculosis from the ascites accompanying atrophic cirrhosis of the liver In the latter case there is usually enlargement of the superficial abdominal veins icterus an enlarged spleen apyrexia and the ascitic fluid has the characteristics of a transudate The occurrence of the two diseases in conjunction may be suspected by the appearance of fever abdominal pain and increased gastrointestinal disturbances in a case of cirrhosis This suspicion will be strengthened if tapping yields a fluid of increased specific gravity and albumin content and showing an increased lymphocytic percentage Evidence of a friction

The presence of non tuberculous complications may greatly lessen the patient s chances In the ulcerative form secondary infection through the damaged intestinal walls with abscess formation may render the condition practically hopeless The symptoms of intestinal obstruction either partial or complete will naturally diminish the probability of survival Fecal fistulae when formed must be looked upon as of very serious significance as recovery seldom occurs in the presence of this complication

In general the prospects are brighter in children and young adults than in infants or those of more advanced years Men are said to show less resistance to the disease than women Those in whom a history of bad heredity as to susceptibility to tuberculosis exists should be considered as having thereby less chance of overcoming the infection

The disease shares with all forms of tuberculosis the tendency to yield cures more frequently in those who are able to devote months or years to the pursuit of health and who can command the best care and the most favorable environment The possibilities as to treatment must therefore be considered in forming an opinion of the prognosis

The duration of the disease in the presence of a miliary tuberculou infection is a matter of weeks The fatal cases of the caseous or fibrous types run their course as a rule inside of a year The development of tuberculous lesions at a later date carries off a considerable proportion of those who have survived the peritoneal infection A conservative estimate of the perma nently cured cases will hardly exceed twenty per cent of the total of all types

Treatment

Until the publication of Koenig s work in 1884 the treatment of tuber culous peritonitis was for the most part confined to palliative measures Following that date there was a rapid adoption on the part of the profe sion of the use of surgical measures in the hope of obtaining a cure of the di ea e In the last years of the century tuberculous peritonitis had come to be considered as lying almost exclusively within the dom un of the urgeon A marked reaction has since occurred against this point of view due largely to the growing recognition of the benefits in all cases of tuberculosis of a systematic and thoroughly carried out dietetic hygienic regime Surgical intervention has by no means been abandoned but the indication for operation have become better defined and more limited

Medical Treatment—In the medical treatment of tuberculous peritonitis rest in bed superalimentation and the fresh air cure are recognized as the most valuable measures The role of medicinal agents and of local therapy is decidedly secondary Rest in bed should be rigorously prescribed during the period of activity of the disease as evidenced by pre ence of a cite

The tuberculin test in tuberculous peritonitis has not yielded dependable results and is condemned by Herzfeld as dangerous The von Pirquet test if negative may be of considerable value in puzzling cases It should be recalled in acute tuberculosis in the terminal stage of tuberculosis and in the presence of severe intercurrent infections in a tuberculous individual a negative von Pirquet test may be obtained

The leukocyte count in peritoneal tuberculosis is rarely markedly increased usually running below 10 000 Cases have been reported however in which a leukocytosis of 15 000 or over was present The urinary findings show nothing characteristic Indicanuria is fairly constant

Too much stress cannot be laid upon the importance of a thorough general examination Both from a diagnostic and prognostic point of view knowledge of the presence or absence of tuberculous lesions elsewhere in the body (lungs glands bones etc) is of the greatest value

Prognosis

Since laparotomy has been advocated as a therapeutic measure in tuberculous peritonitis a renewed interest has been manifested in the early diagnosis and in the ultimate outcome of this disease The general result has been that the idea of a uniformly fatal outcome has been abandoned This is due to the fact that operation has enabled us to classify definitely as tuberculous many mild and localized forms of the disease which at an earlier period because of their very mildness would have been termed idiopathic peritonitis Observation of the course of such cases has shown indubitably that tuberculous peritonitis may be permanently cured Prognosis in the individual case remains however difficult and uncertain There is a paucity of statistics compiled from cases which have been observed over a sufficient number of years to give assurance that the end result has been seen The form of the disease is too seldom stated and the cause of death is rarely given

Certain important factors in prognosis must be considered in each individual case Of these the most vital is the presence or absence of active tuberculous lesions elsewhere in the body Relatively few patients die directly from tuberculous peritonitis In cases which end fatally death in nearly ninety per cent is due to tuberculous lesions elsewhere in the body (Schlimpert) Of such lesions the pulmonary are the most common

The form of the disease must be taken into consideration The chronic ascitic form is that yielding the highest number of recoveries The fibrous form ranks next The outlook in the caseous and ulcerative form when it is diffuse is very unfavorable All the localized forms when uncomplicated offer a reasonable chance of recovery

unsound because of the known unfavorable effect of the X rays on young connective tissue cells and hence on curative fibrosis The injection of air nitrogen oxygen and of various antiseptic agents (iodin camphorated oil etc) into the abdominal cavity has proved useless and dangerous

The use of tuberculin has apparently not been given extensive trial in recent years The earlier results were not favorable and in certain instances rapid extension of the disease was apparently directly traceable to this source

Surgical Treatment—Paracentesis is always indicated in those case where the size of the effusion directly threatens life by interference with respiration It is often necessary also for diagnostic purposes to obtain a specimen of the ascitic fluid As a curative agency tapping is of value in certain chronic ascitic cases in which there appears to be no tendency to spontaneous regression of the fluid Repeated removal of the fluid will sometimes hasten the natural process The possibility of puncturing or of lacerating an intestinal loop adherent to the abdominal wall should be borne in mind and guarded against as much as possible by repeated preliminary observations of the extent of tympanitic zones determined by light percussion

Laparotomy in tuberculous peritonitis may be indicated (a) as a directly curative agency (b) for the purpose of removing the primary focus of infection (c) because of the occurrence of secondary complications (intestinal obstruction abscesses due to mixed infection)

The experience of the last thirty five years as reflected in the statistics of the results of laparotomy upon cases of tuberculous peritonitis has resulted in a fairly unanimous agreement only as to the need of careful selection of cases The most definite benefit has been seen in cases of the chronic ascitic form The value of the procedure in the dry fibrous form is questionable The caseous form is by most authors considered as unsuitable for operation

The lack of a common point of view by the various surgeons who have compiled statistics makes it extremely difficult to form a just estimate of the results The standards as to what constitutes cure of the disease (length of period of observation) are especially variable Moreover there is little statistical data bearing upon the results of purely medical treatment so that comparison is very difficult

A multitude of theories has been advanced to explain the beneficial effect of laparotomy upon tuberculous peritonitis but the question is still undetermined The emptying of the ascitic fluid is supposed by some to result in a more liberal blood supply to the relaxed peritoneal membrane Wegner has shown experimentally that simple laparotomy is followed by a hyperemia of the peritoneum The role of light and air in producing this

fever gastrointestinal disturbances etc and should be continued thereafter until the patient s weight is up to normal Resumption of activity should be made very gradual so as to extend over a period of many months during which time the patient should be under close observation

The character of the diet will necessarily be altered by the nature and prominence of the gastrointestinal symptoms which may be present In general a lactovegetarian diet will be found most suitable as a basis to which an accessory diet of moderate amounts of meat and fish and raw eggs should be added The milk and eggs should be increased up to the patient s tolerance

The open air cure as carried out in the large sanitoria for tuberculous patients is a valuable aid in maintaining the patient s nutrition and resistance to the disease Sanitorium care when facilities exist for surgical intervention if the necessity arises is to be recommended when it is not feasible it should be approximated as closely as possible in the general hospital or in the patient s home High mountain climate is recommended as favorable in these cases

As an adjuvant heliotherapy is well worth a trial in all cases it is probably most effective in the clear atmosphere of higher altitudes The exposure of the abdomen to the direct rays of the sun should be started very gradually and increased a few minutes each day

Of the general medicinal agents recommended the various forms of iodin seem to be most favored No convincing data is at hand however and judging by analogy with pulmonary tuberculosis the use of these remedies is not without danger The use of strong purgatives in the constipation which characterizes many of these cases should be avoided if possible The use of an ounce (30 c c) of mineral oil night and morning and an occasional mild laxative is preferable to the employment of stronger purgatives Oil and glycerin enemata may be of value

The milder forms of diarrhea are usually self limited when intractable the presence of tuberculous enteritis should be suspected In the milder cases bismuth laudanum or paregoric will be effective but should be employed only if the diarrhea is sufficiently marked to constitute a drain on the patient s strength In severe cases good results though temporary have been reported following intravenous injections of calcium chloride (5 to 10 c c of a five per cent solution)

A host of special therapeutic agencies have been employed in tuberculous peritonitis in an attempt to alter by direct action the pathological lesions within the abdomen The various applications to the skin over the abdomen iodin, collodion soap etc need only be mentioned The irradiation of the abdomen with the X rays has not met with sufficient success to warrant its use As Hertzler has pointed out this form of therapy is theoretically

Echinococcus Disease of the Peritoneum

The development of echinococcus cysts of the peritoneum constitutes one of the rarer abdominal diseases In this country it is seen chiefly among the Greeks in the foreign settlements of our larger cities The etiology and pathology are discussed in Vol V

Symptoms

The disease is characterized clinically by a long stage of latency by a period in which pressure symptoms predominate and by terminal cachexia

The rupture of a hydatid cyst into the peritoneum may produce marked symptoms but as Deve has shown by a careful analysis of case histories it may be unaccompanied by any noteworthy manifestations The phenomena seen in the first instance include abdominal pain shock vomiting and the sudden development of a striking urticarial eruption When the ruptured cyst is situated in the liver a bile containing peritoneal effusion (choleperitoneum) is found If infection of the cyst precedes its rupture a fatal general peritonitis results otherwise the irritative and toxic manifestations due to the chemical constituents of the fluid subside

A latent period of a number of months or years follows before the implanted peritoneal cysts have developed dimensions sufficient to cause symptoms Gradual enlargement of the abdomen with vague discomfort and a sensation of pressure and weight are usually the first symptoms noted by the patient Pressure on the intestines may lead to digestive disturbances (nausea gas constipation colicky pain) The pelvic localization of the disease may be signalized by irradiating pains down the thighs by disturbances of urination dysmenorrhea and dyschezia In rare cases labor has been interfered with by such pelvic tumors In the advanced stage of the disease the marked enlargement of the abdomen may interfere with respiration

Hydatid cachexia in these cases is of gradual onset The duration of the disease is very variable Death is frequently due to the effects of a cyst located elsewhere in the body or as a result of abdominal complications (suppuration of a cyst intestinal obstruction etc) In some instances life may be prolonged for many years

Diagnosis

The clinical diagnosis of the disease is extremely difficult in most cases This is partly due to the rarity of the disease in most parts of the world It should be always considered however in the differential diagnosis of any

effect is not clearly determined Such increased vascularization may well stimulate the fibrosis going on in the tuberculous lesions Healing by fibrosis has been shown by histological examination of lesions in reoperated cases to have occurred in the interval since the first operation

A conservative course at the present time is advocated by many authorities Laparotomy for the sake of its curative effect is to be undertaken only when a thorough trial of a medical regime has not checked the disease or when no evidences of improvement are seen It is then often of distinct value in the chronic ascitic form occasionally of benefit in the fibrous type but offers little chance of success and is often harmful in the caseous variety An exception can perhaps be made in the last instance to include cases in which a definitely localized form of the disease is present and those in which marked ascites or a sacculated purulent exudate is present Operation is contraindicated in the presence of extensive tuberculous lesions outside of the peritoneal cavity and in infants under one year

The operation performed is usually a simple opening of the peritoneal cavity by a midline incision below the umbilicus evacuation of the ascitic fluid and closure without drainage The immediate operative mortality is not high 7 5 per cent The chief complications which occur are suppuration of the abdominal wound the formation of fecal fistulae and secondary infection of the peritoneum following injury to the intestines The avoidance of all intraabdominal manipulations will reduce these dangers

The removal of the primary focus of tuberculous infection in cases of peritoneal tuberculosis which have resulted by extension is strongly advocated by some surgeons The fallopian tubes have very frequently been removed and the tuberculous cecum has been resected Where the primary lesion is advanced and the peritoneal involvement is at an early stage such a procedure is probably justified The tubes should never be removed however unless their involvement by the tuberculous process is so extensive as to preclude all possibility of their return to normal When the caseous or fibroid form of tuberculous peritonitis is present attempts to remove the primary focus would usually be hazardous and would offer but slight chances of benefit

Surgical intervention is of course urgently indicated in cases complicated by acute intestinal obstruction Its advisability in the presence of the moderate obstruction symptoms which often appear in the fibrous form is less evident The operator when confronted by the hopelessly adherent and matted down mass of intestinal coils is often unable to afford any relief to the condition The presence of definite purulent accumulations indicates operation though the outlook for such cases is only slightly improved by the procedure

propagation of columns of cancer cells through the intervening tissues along connecting lymphatic channels Where the carcinoma grows through the peritoneum its free surface is bathed by the peritoneal fluid The fluid currents carry off and disseminate throughout the peritoneal cavity cancer cells which may become implanted on the membrane and set up carcinomatous nodules The pelvic peritoneum is especially apt to be affected by such metastases The omentum also is frequently infiltrated and may be transformed into a thick sheet of carcinomatous tissue The mesenteric and retroperitoneal lymph glands usually show some degree of involvement

Peritoneal cancer may take the form of scattered sessile nodules of large thick plaques of massive irregularly rounded tumors or of diffuse sheets and lumps of soft colloid material When a general carcinomatosis is present the peritoneum may be thickly studded with grayish granules resembling tubercles A scirrhous type is sometimes seen in which the parietal peritoneum is greatly thickened and the intestines and omentum are bound down by bands and sheets of the connective tissue stroma

The uninvolved peritoneum usually shows evidence of a mild inflammatory reaction The luster of the membrane is lost capillaries are injected and delicate fibrinous adhesions unite the surface of the tumors with the surrounding structures Ascites is a marked feature of peritoneal cancer The fluid may be lemon colored and clear or opalescent but it is more frequently blood tinged or frankly bloody

Histologically the tumors in the peritoneum show a tendency to reproduce the type of the primary carcinoma Simple adenomatous and papillary *arrangements are commonly seen in the metastatic growths* When the primary tumor arises from structures containing goblet cells (stomach ovary intestine) the multiplication of these cells in the peritoneum is responsible for the production of large soft colloid masses containing only a slight framework of stroma

Endothelioma—Peritoneal endotheliomata are primary malignant tumors analogous to the endotheliomata of the pleura Macroscopically small nodules flat plaques or more massive and softer tumors are found arising from the peritoneal membrane The distribution of the endotheliomatous tumors is *widespread The individual nodules may* show a tendency to be localized along the lymphatic channels A distinction from carcinoma can be drawn from the fact that the endothelioma appears to have originated simultaneously at a number of widely separated points rather than to have been disseminated from a primary tumor The nodules show less tendency than carcinoma to invade the surrounding tissues by *cellular infiltration* their method of extension is more by pressure

The differentiation from tuberculous peritonitis may frequently be

case of multiple abdominal tumors of unknown etiology Peritoneal neoplasms and the caseous form of peritoneal tuberculosis are most easily confused with it

History of residence in an infected country evidences of a cystic enlargement of the liver or spleen very gradual appearance of the abdominal symptoms and of the tumors their cystic character and their multiplicity are significant diagnostic point

In the case of larger cysts fluctuation may often be present In rare cases a peculiar thrill is felt on palpation due probably to the impact against each other of the daughter cysts To those who are experienced in the diagnosis of this disease it may yield conviction The presence of a marked eosinophilia (5–10 per cent) is good confirmatory evidence The complement fixation tes if available is probably decisive when positive Diagnostic aspiration is dangerous and should not be done Exploratory operation with removal and examination of a smaller cyst is decisive

The use of the X ray will be of value in determining the presence of pulmonary involvement It would seem that help might also be obtained in localizing the abdominal tumors from plates taken after the production of pneumoperitoneum

Treatment

Prophylaxis consists primarily in the avoidance of infected water supplies fresh fruits and vegetables in regions in which the disease is known to exist In enucleation of hydatid cysts of the liver the greatest care should be taken to avoid contamination of the peritoneal cavity with the infective cyst contents

The surgical treatment of the peritoneal cysts consists in their complete removal unruptured when possible This may necessitate repeated laparotomy In extensive involvement it is rarely successful Incomplete operative removal is sometimes followed by rapid spread of the disease

Malignant Tumors of the Peritoneum

Pathology

Carcinoma —Carcinoma of the peritoneum is always secondary to cancer elsewhere in the body Usually the primary tumor lies within the abdominal cavity (stomach ovary intestine pancreas etc) but it may be situated at a distant point and the peritoneum be involved by hematogenous metastases Cancers of the abdominal viscera involve the peritoneum either by growth of the mass to the surface of the serous membrane or by the

Symptoms

The symptoms due to a primary tumor outside the peritoneal cavity frequently precede the evidences of malignant disease of the peritoneum In primary new growths of the serous membrane however and in cases in which a primary visceral tumor has remained latent the clinical picture which results from the peritoneal involvement appears as the beginning of the patient s illness Abdominal discomfort or pain tumor ascites and cachexia are the chief manifestations of malignant tumors of the peritoneum

The pain varies greatly with the site of the disease Tumor nodules or masses at the root of the mesentery appear to occasion greater suffering than those less closely associated with the sympathetic ganglia In many instances the pain is intermittent and colicky and bears a relationship to the digestive cycle which suggests that interference with intestinal motility by the tumor growth is its chief cause

Tumor masses are usually early made out in those cases in which a visceral tumor has involved the peritoneum by extension In primary tumors of the peritoneum pain and ascites may long antedate the presence of any palpable mass Malignant growths in general form hard uneven masses often large enough to cause irregularities in the surface contour of the abdomen In secondary tumors a main tumor mass is usually palpable whose situation and mobility suggest the organ from which it has developed Late in the course of the disease lesser nodules may be felt elsewhere in the abdomen In colloid carcinoma the consistency of the tumors formed is less firm and areas of semifluctuant consistency may be felt

The tumor masses may be masked by the practically constant ascites which characterizes the disease The effusion is usually considerable causing a well marked distention of the abdomen The ascitic fluid is usually relatively free within the peritoneal cavity so that shifting dullness and fluctuation wave are readily obtained upon examination In the majority of cases tapping yields a blood tinged or frankly bloody fluid though there are many exceptions to the rule

Loss of weight and strength and marked anemia of the secondary type appear early in these peritoneal neoplasms and constitute strong evidence of the malignant nature of the process Weakness soon confines the patient to his bed Signs of extension of the disease beyond the peritoneum appear in the later stages Invasions of the portal vein or of the vena cava by the tumor growth may produce a caput medusae or marked edema of the lower extremities The inguinal lymph glands enlarge and small hard nodules may appear in and under the skin In the terminal stages emaciation is extreme the face shows an ivory white pallor there is edema of the feet and ankles.

difficult especially as the larger tumor masses may have caseous centers Ascites is constant The fluid is usually frankly bloody or blood stained It contains considerable amounts of fibrin The albumin content is high four to six per cent Tumor cells may sometimes be found microscopically

Agreement among pathologists has not been reached as to the histogenesis of these tumors The cellular structure is remarkably varied and the resemblance to carcinoma or to sarcoma may be equally striking The fundamental cell type in the younger tumors is a flat endothelioid cell These cells are apparently not derived from the surface endothelium but from within the serosa The proliferation of the cells lining the lymph channels which has been observed points to these as a point of origin In the tumor tissue the endothelioid cells lie in solid columns or in long strands in a stroma of connective tissue Sometimes a hollow tube resembling glandular tissue is seen Occasionally the protoplasm of the cells is fused to form a veritable syncytium

Sarcoma —The peritoneum is seldom directly involved by either primary or secondary sarcoma Rarely there occurs a proliferation of sarcomatous nodules throughout the peritoneal cavity as a part of a general sarcomatosis A few cases of primary sarcoma of the omentum have been described The involvement of the omentum was in some instances diffuse so that a single large mass of reddish gray friable tumor tissue resulted In other cases a globular lobulated mass was located in some portion of the omentum Invasion of adjacent structures (gut bladder) has been noted There is a tendency to hemorrhage in the tumor tissue with formation of blood cysts Hemorrhagic ascites is usually present

Pseudomyxoma —Following the rupture of a pseudomucinous ovarian cyst or much more rarely of a cystic occluded appendix there may occur in the peritoneal cavity the development of a very large amount of gelatinous material loosely held together in sheets and rolls by a delicate stroma of connective tissue The predominance of the homogeneous colloid material the absence of cellular structures engaged in the production of such a secretion and the evidence of peritoneal irritation (vascularity fibrin formation) make it difficult to state whether the whole process is to be classed among the new growths or as a reactive phenomenon on the part of the peritoneum to an irritant substance contained in the cysts The history of cases in which this condition developed following removal without rupture of ovarian cysts suggests the recurrence of a malignant growth The assumption that a mild but tenacious chronic infectious process is the cause both of the cysts and of the peritoneal phenomena is unsupported by proof but accords best with our data on the condition

Benign Tumors of the Peritoneum

Pathology

The benign new growths of the peritoneum are all rarities The chief varities observed are lipomas and various types of cysts Lipomas may develop in the omentum in the mesentery and by hypertrophy of the appendices epiploicae The entire omentum may enlarge rapidly so as to form an apron of fat several inches thick which displaces the viscera upwards and embarrasses respiration and the heart The new growth in these instances contains an admixture of adipose and of myxomatous tissue so that the term myxolipoma is applicable In other cases a lipoma may develop in a portion of the omentum which is contained in a hernial sac without any change taking place in the remainder *Large lipoma may grow in the* mesentery of the small intestines or in the mesocolon Terrillon has reported one which weighed twenty nine kilograms

Peritoneal cysts may develop in areas subject to chronic irritation as a result of inflammatory changes or as a sequence to the encapsulation of hematomas or exudates The more constant varieties however are those which have their origin in congenital displacements of embryonal tissue Dermoids have been described They are epidermoidal sacs and have usually been found in the midline in the urachus or in the retroperitoneal tissues The *enterocystomas according to Hertzler arise from snared off* sections of fetal gut epithelium derived from Meckel s diverticulum the omphalomesenteric duct or from other diverticula of the intestines These cysts are usually found in the anterior abdominal wall or in the mesentery Their walls may retain a double layer of muscle fibers They are lined with columnar epithelium which in typical cases may form villi Lymphatic cysts of the mesentery have been explained as retention cysts due to obstruction of mesenteric lymph channels or to cystic degeneration of lymph glands It seems more probable as Hertzler has pointed out that they are homologous with the lymph cysts of the neck and axilla and probably arise from congenital anlage in the mesentery Their walls are of connective tissue and contain nodules of lymphatic tissue muscle fibers and elastic tissue The cyst fluid may be either clear or chylous in some instances it is bloody Single globular tumors the size of an egg may be found or large polycystic masses

Symptoms

Many of the benign tumors cause no marked symptoms unless they develop to a large size The very large lipomas may so overcrowd the abdomen as to interfere with the respiratory movements of the diaphragm

Intestinal obstruction peritonitis acute colitis, pneumonia decubitus are common complications which hasten the fatal ending The course of the disease varies from a few weeks when an acute general carcinomatosis is present up to a year or more in cases in which extension of the process is less rapid The constitutional effects in cases of pseudomyxoma peritonei are much less marked than when the more definitely malignant tumors are present and the duration of this disease is correspondingly longer

Diagnosis

When the diagnosis of a primary visceral tumor has been made there will usually be little difficulty in interpreting correctly the development of symptoms indicating extension to the peritoneum The primary malignant tumors of the peritoneal membrane may offer greater difficulties They are most readily confused with tuberculous peritonitis and with echinococcus disease of the peritoneum In acute carcinomatosis the difficulty may still remain when the peritoneal cavity has been opened for the small cancerous nodules may strongly resemble miliary tubercles and histological examination may be required to differentiate them

The finding of tuberculous lesions or of carcinoma elsewhere in the body may clear up the difficulty A distinctly febrile course is more common in tuberculosis Frankly hemorrhagic ascites is usual in malignancy and rare in tuberculosis Animal inoculation of the fluid may yield a decisive result in tuberculosis The inguinal glands are frequently involved by metastases from peritoneal tumors If enlarged one should be excised for diagnosis The extreme chronicity of echinococcus disease the cystic character of the tumors and the results of the complement fixation test serve to differentiate this condition

Treatment

When the character of the tumor is unknown exploratory laparotomy is justifiable Intervals of several years before recurrence have been obtained by excision of sarcoma of the omentum The removal of the primary pseudomucinous ovarian cysts has in certain instances been followed by an apparent cure of an early stage of pseudomyxoma peritonei Metastases to the peritoneum from papillary cyst adenomata of the ovary have regressed following excision of the primary growth When the disease is far advanced such an outcome cannot be expected Paracentesis should be employed when necessary to relieve distention Cancerous implantation along the needle track may follow The treatment otherwise is purely symptomatic

operat on of demonstrating their extraperitoneal origin The inflated colon may be shown by percussion to lie anterior to the tumor mass A fluoroscopic examination after a barium meal will yield proof of the same fact Bulging in the back the marked degree of fixation of the tumor and evidence of its pressure on the ureters are all confirmatory of its retroperitoneal position

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In general omental tumors cause less disturbance than those situated in the mesentery. Cysts of the mesentery may cause pain and disturbances in intestinal motility apparently by interference with sympathetic fibers. Sudden enlargement of such cysts may lead to direct pressure upon the gut with consequent intestinal obstruction.

Diagnosis

The symptoms are not sufficiently characteristic to be an aid to diagnosis. When a palpable tumor can be made out, its relation to the intestines and its mobility will help to localize it. Mesenteric tumors lie behind the intestines as determined by percussion or the X ray and have a marked degree of mobility especially laterally which distinguishes them from retroperitoneal masses. Omental tumors give a flat note on percussion since they lie directly against the anterior abdominal wall. The nature of the tumors cannot be diagnosed without exploratory operation.

Treatment

The treatment consists in the surgical removal of the tumors when possible. Inoperable cysts may require marsupialization.

Tumors of the Retroperitoneal Space

The tumors of the retroperitoneal space are not derived from the peritoneal membrane but from a clinical point of view it is useful to consider them briefly at this point since they must be differentiated in the diagnosis of true peritoneal neoplasms.

Lipomas, lipomyxomas, sarcomas and teratomas may develop in the retroperitoneal space. The first three form one group whose point of origin is the paravertebral connective tissue. They are characterized by a tendency to rapid growth and attain large size. Their consistency is soft. Histologically they are as a rule mixed tumors. The lipomas usually contain areas of myxomatous tissue and show a marked tendency to sarcomatous degeneration. In the sarcomas myxoid and lipomatous tissue may be found. Their growth pushes the colon forward and may produce a bulging in the back. Pressure on the ureters may result in hydronephrosis. The vena cava may be compressed with resulting edema. Ascites sometimes develop. Teratomas are rounded firm tumors showing a less infiltrative type of growth than the sarcomas.

The relation of these tumors to the colon is the chief means short of

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CHAPTER X

BRIGHT'S DISEASE

By HENRY A CHRISTIAN

PART I

GENERAL CONSIDERATIONS

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CHAPTER X

BRIGHT'S DISEASE

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PART II

CLINICAL ASPECTS

PART I

GENERAL CONSIDERATIONS

INTRODUCTION

Definition — Bright's[1] disease may be defined for clinical purposes, as a disease in which the kidneys show diffuse, progressive degenerative and proliferative lesions however, Bright's disease involves the entire body mechanism and is not confined to the effects of renal lesion or renal function The term nephritis, focusing attention as it does on the kidney, does not seem so satisfactory to this author for clinical use as the term Bright's disease, a term, which only in an historical sense implicates changes in the kidney as the sole or even the dominant feature of the symptom complex or disease and so it can be used for a disease affecting the entire body Actually Bright himself described numerous changes other than those he noted in the urine and in the kidney

In the preceding definition the plural noun *kidneys* excludes from Bright's disease unilateral kidney lesions In it the word *progressive* is used to exclude those slight degenerative lesions so frequent in infectious diseases in which with albuminuria and cylindruria there is no evidence of impaired renal function, and the kidneys quickly return to complete integrity after the subsidence of the symptoms and signs of the disease The word *diffuse*, is used in the sense of lesions widely scattered throughout the substance of both kidneys It does not apply necessarily to a lesion involving renal structures uniformly, the lesion may be focal in distribution with scattered areas of changed and intervening portions of practically unchanged or normal structure This usage is quite in accord with a dictionary definition of diffuse widely spread or diffused extended dispersed, scattered It does not exclude however a general or even uniform involvement of all portions of the kidney

As indicated by the definition ordinarily both degenerative and proliferative changes are found in the kidneys of patients dead of Bright's disease although often the one or the other has dominated the picture In the same way it is usual to have all of the kidney components show departures from normal however one component may be so much more strikingly abnormal than the others as to justify the pathological terms of interstitial glomerular parenchymatous or vascular nephritis Of all the kidney structures glomerular lesions influence the clinical picture to the greatest degree there is what this author has termed a glomerular dominance-

The definition just given excludes acute inflammatory lesions, acute pyelonephritis often unilateral in their earlier stages as is true also for nephrolithiasis and neoplasm of the kidney It does not exclude the subsequent degenerative and proliferative changes that may develop from pyelonephritis and nephrolithiasis to cause what clinically is a variety of chronic Bright s disease a form included in the author s classification and subsequently discussed in Part II of this chapter

Nephritis still is the best word we have for the *pathological lesions* in the kidneys of patients with Bright s disease Its use however has aroused a discussion of inflammation versus degeneration in the pathological process with the suggestion that nephritis be used for the inflammatory process and nephrosis for the degenerative process to which there can be no objection other than that in the great majority of the lesions both inflammation and degeneration are in evidence It is true that the ending itis has come to connote in its general usage inflammation However etymologically this is not correct it is a usage that has developed relatively late in the history of medical nomenclature[3] In the early Greek itis meant of about concerning and so nephritis seemed to mean only of about or concerning the kidney and to convey the idea of disease of the kidney required an additional word such as nosos or phthisis and we find in classical Greek such usage as nosos nephritis phthisis nephritis Similarly the ending -osis meant full of and so nephrosis meant full of kidney or kidney substance not degeneration of the kidney However we need not quibble we can still use nephritis in its later meaning implying inflammation of the kidney since broadly speaking inflammation is defined in modern pathology as the reaction to injury and includes degenerative changes as well as cellular infiltration and tissue cell proliferation cell and tissue degeneration is an important part of the process of inflammation However under nephritis at the present time we do not include such a typical inflammatory lesion as renal suppuration whether focal as in abscesses or diffuse as in acute nephropyelitis Nephropathy is a term that has been suggested for the pathological lesion of Bright s disease but it is not satisfactory becau e it is too inclusive strictly speaking meaning any lesion of the kidney Nephrosis is a term which some use for a particular clinical type of Bright s disease and for a form of lesion that is found in some of these patients that usage however is not satisfactory as will be discussed later in this chapter

Historical

Dropsy is such an obvious condition that its presence and its meaning neces sarily must have interested physicians from earliest times and yet our existing knowledge as to its causes and its treatment is not very old William Withering s interest in dropsy lead to his studies of the use of digitalis and the publication

in 1785 of his book entitled "An Account of the Foxglove and some of its Medicinal Uses with practical Remarks on Dropsy and other Diseases' Another landmark in progress of knowledge about dropsy was Richard Bright s descriptions of Cases illustrative of some of the appearances observable in the Examination of Diseases terminating in Dropsical Effusion and first of the Kidney" published in 1827 as part of his Reports of Medical Cases Selected with a View of Illustrating the Symptoms and Cure of Diseases by a Reference to Morbid Anatomy "[1]

From a very early time observation of the urine of patients was an important item in the procedures of doctors That albumin can be found in the urine of some patients by the simple expedient of boiling the urine long has been known, but its real significance remained only a matter of surmise until the studies of Bright Bright believed that albumin in the urine along with the presence of dropsy pointed to disease of the kidney[1] This he sought to prove, and succeeded in doing so by studying patients showing these conditions and, when they died autopsying them to see whether or not their kidneys appeared abnormal and how In his 1827 book appeared a clinical description of 24 patients, 18 fatal By this report and other studies published by him in later years Richard Bright demonstrated that kidney disease was evidenced by the presence in the urine of albumin and that many of these had kidney disease as the cause of dropsy rather than any one of other possible causes for this disability Richard Bright in his reports described accurately a great many features of what became recognized later as nephritis or what many subsequently have preferred to call, in his honor Bright's disease The publication of Richard Bright in 1827 marks the beginning of our real knowledge of this disease and it is surprising how much of the symptomatology of this form of kidney disease, as we know it today, was recognized and described by Bright in his study of 1827

Bright in 1827 described and pictured kidneys from patients with nephritis, but he did not record any studies of their microscopical appearances, so his knowledge of their pathology was incomplete In 1851 Frerichs[139] using then the term Brightsche Krankheit published a study in which he took a unitary view of the renal lesions of Bright s disease regarding the various forms of the kidneys, as he saw them as stages in a single process which began as acute nephritis and ended as a small granular kidney or the chronic interstitial nephritis of a later date This unitary view seemed to have prevailed until about the time of Weigert s studies of 1879[140] which showed the fallacy of this conception of Frerichs Weigert regarded what Frerichs had considered to be different stages in a single process as types of renal lesions representing the varying reactions of renal structures of varying resistance to the action of injurious substances of varying strength acting during varying periods of time Weigert abandoned the idea of a unitary process producing at different stages certain appearances in the kidney

in favor of several different processes each with characteristic gross and histological appearances at different stages in the progression of each process an idea which in general is more in accord with present day conception of the pathology and pathogenesis of Bright s disease particularly as concerns glomerulonephritis than was the unitary concept of Frerichs

After Weigert s publication the next advances came chiefly in more complete and minute studies of the pathology of Bright s disease which among other things emphasized changes in the glomeruli as of primary importance in certain forms of Bright s disease and changes in the renal blood vessels particularly the arterioles as the chief cause of the changes developing in certain other forms of Bright s disease These studies separated the kidneys of Bright s disease into two main divisions 1) those developing in the sequence of glomerular lesions glomerulonephritis and 2) those developing in the sequence of arteriolar lesions vascular nephritis divisions which had more differences than similarities in etiology pathogenesis progression and incident clinical syndromes

From Bright in 1827 through the XIX Century studies of Bright s disease remained largely clinico-morphological Early in the present century interest shifted and now began a series of studies of experimental renal lesions lesions produced in animals analogous to those observed in man These have thrown light on the etiology and pathogenesis of the lesions of human Bright s disease and on the physiology of the kidney although the exact disease in man particularly in its chronic forms has not been reproduced in animals by experimental methods

Gradually studies of experimental nephritis took on a more functional aspect How the urine is formed by the kidney largely has been elucidated Cushny s book of 1917[10] is a landmark in our understanding of the physiology of the kidney while the securing and quantitation of the contents of individual glomerular spaces and tubules by Richards and his pupils[4 8 11 12] in 1924 and in subsequent years demonstrated directly what Cushny had assumed the filtration activity of the glomeruli and the absorptive activity of the tubules in the formation of urine To this at a later date has been added proof of certain excretory functions of the tubules to give us finally a quite satisfactory and apparently a complete understanding of the physiology of the normal kidney

In this same period commencing early in the second decade of the present century techniques for the study of function in the diseased human kidney have been developed A very important one of these is the phthalein test developed by Rowntree and Geraghty[441] in 1912 Another is derived from the development especially by Folin and his pupils[44] at about this same time of methods for quantitating accurately in small amounts of blood various protein constituents quantitative methods added to by Van Slyke and his associates and by others so that now almost all of the constituents of blood and urine can be quantitated

with a facility and accuracy that make these methods applicable to the daily work of all well organized clinics.

Another advance has come more recently by developing clinical methods for differential function studies of patients so that a fairly accurate quantitation of glomerular and tubular activities has become possible, advances in which Homer W. Smith[7, 8] has played an important role. Applying these methods the clinico-morphological studies of the XIX Century have been extended by the chemico-functional studies of the XX Century. Finally an important recent advance has come from electrophoretic methods of Tiselius for analysis of the proteins of blood and urine, methods which in these relationships are being applied now very profitably in our clinics in the study of various phases of Bright's disease as a sequence to the important studies of proteins by Edwin Cohn and his associates at the Harvard Medical School.

Before describing the several forms or types of Bright's disease, certain general considerations will be taken up in order better to understand the descriptions of them and to save repetition where the same data are needed in an understanding of several or all of the varieties of Bright's disease. To understand the abnormal functional activities of the kidney in Bright's disease a knowledge of its normal structure and function is needed, so I will proceed next to a description of normal renal structure and function.

Normal Renal Structure and Function

It hardly seems necessary to describe in detail in such a chapter as this the structure of the kidney. However, for a better understanding of renal function a brief description of the main features of renal structure is needed and will be given.

Mesodermal in origin the kidney in numerous respects differs from the secreting glands of the body, which are epidermal in origin. The kidney is built up of a very great number of units[4], each of the same structure, held together by a loose connective tissue in which lie the closely interrelated blood vessels. Blood vessels enter the glomeruli to become their most important structure and they surround the tubules closely. The unit of the kidney is made up of a glomerulus connected with a long tubule running a complex course and lined at different levels by cells of differing structure. These units are intertwined in a complex fashion with the glomeruli and the first and fourth parts of the tubule constituting the cortex and interpyramidal parts of the kidney and the descending and ascending limbs of the loops of Henle, the second and third parts of the unit, and the straight and collecting tubules, the fifth part of the unit, composing the pyramids of the kidney. The first and third parts of the tubule are convoluted, the other parts are not convoluted but undulating or straight except for the bend where

the descending limb turns back into the ascending limb By methods of teasing the best views of this complex structure in both normal and pathological kidneys have been obtained

The kidney has an arrangement of circulation not found in any other organ The majority of the blood vessels coming to the kidney divide and subdivide with progressive decrease in size down to branches of the order of arterioles Many of these become the afferent arterioles of the glomeruli through them a very large part of the blood coming to the kidney flows into the glomeruli As soon as the afferent arteriole reaches the glomerulus it subdivides into capillary loops which in turn come together to discharge their blood into an efferent arteriole Efferent arterioles unite to form larger blood vessels these in turn subdivide again into arterioles and then capillaries which are distributed in the interstitial tissue about the tubules Finally from this intertubular capillary system the blood flows into venules and veins to form eventually the main renal veins that empty into the inferior vena cava By such routes most of the blood that goes through the kidney flows first through glomeruli and after this to the narrow spaces between the tubules However there are certain anastomoses which short circuit some blood direct to the intertubular spaces without its going through glomeruli In the normal kidney this part carries only a small part of the renal blood flow, in pathological conditions these short circuiting channels increase in number to carry to the intertubular spaces more blood which has not passed through the glomeruli than happens in the normal kidney

This vascular arrangement makes possible variation in intraglomerular pressure by constriction of the afferent and efferent arterioles to influence blood flow through the glomerulus and consequently variation in the filtration of water and other filterable constituents from the blood into the tubule in addition to the effect of various factors that change blood flow to the kidney through the renal arteries and their larger branches About the arteriole of the glomerulus are groups of cells of special structure richly innervated which are believed to have a part in changing the caliber of the efferent arteriole[6, 7] and thus exerting some control over blood flow through the glomerulus These structures resemble that of digital glomi and glomus tumors Some believe they undergo hyperplasia and play some role in the mechanism of hypertension Others describe degenerative changes in them in advanced stages of hypertension and suggest that their role in hypertension is a negative one In the human kidney they are not easy to demonstrate requiring special technic and very fresh tissue

In the frog some glomeruli are seen to fill with blood while others are empty and even the individual capillary loops within the glomerulus are seen to intermit in blood flow[8] In man according to the studies of Smith[9] blood flow in the glomeruli appears not to undergo these fluctuations observed in frogs by Richards and his associates

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individual glomeruli and in individual tubules at the same time as determining quantitatively these substances in excreted urine There still remains very general agreement to Cushny s modern theory of the mechanism of kidney activity except as to his belief that tubular function was only absorptive Later work indicates that tubules can excrete Certainly they do so in the formation of urine by the aglomerular kidney of some fishes[13 14] Marshall and his coworkers[15 16] showed that phenol red was excreted or secreted by the tubules the same has been proven too for some complex organic iodine containing compounds[9 17 18] These however are substances foreign to the body but if they can be excreted by the tubules this suggests the possibility of tubular excretion of substances normally present in the human body This seems to be true of creatinin part of that which appears in the urine seemingly being excreted by the tubules Also there is evidence that in some pathological human kidneys there are functioning tubules no longer connected with a functioning glomerulus possibly these are functioning like tubules in the aglomerular kidneys of certain fishes i e excreting Granted that tubules can contribute to the urine something by excretion the fact remains that urine formation is chiefly the result of glomerular filtration and tubular reabsorption it can not be said however, that nothing enters the urine except as the result of these two processes

Filtration through the glomerulus like filtration through filter paper necessarily depends on several factors on difference in pressure on the two sides of the membrane on the character of the membrane on the nature of the fluid to be filtered[1] The influence of variations in the character of the membrane often is underestimated For instance variations in oxygen supply may cause marked changes Again variations in the blood plasma are very important The normal renal membrane holds back the large molecules of the colloids of the blood serum These in turn exert a considerable osmotic pressure 25 to 35 mm of mercury, and thus may retard filtration

By filtration a fluid very different from urine is supplied to the tubules How great this difference is and how much of a part is played by absorption in the tubule is seen from the following table taken from Cushny's book[10] (see Table I)

This table shows the necessarily large amount of fluid and solids that needs to be reabsorbed in the tubule in order to furnish one liter of urine and emphasizes how le ions in the tubules could cause marked disturbance in renal activity Urea ammonium phosphate and sulphate appear in the urine in much higher concentration than in the blood plasma, uric acid and potassium are less concentrated sodium and chloride show slight change

In absorption in the tubules there are according to Cushny[10] two groups of substances threshold bodies useful to the body which are taken up in part by the tubules and returned to the blood and no threshold bodies of no further service to the body which are not reabsorbed Substances in the tubules which

The blood flow through the kidney is remarkably great[4] It is said that an amount of blood five times the weight of the kidney may traverse its vessels in one minute and that all of the blood in the body may pass through the kidneys in as short a time as three or four minutes Studies on man using the inulin clearance test indicate a glomerular blood flow of 125 c c per minute[9] Any factors influencing such an enormous blood flow to and through the kidney, and particularly to and through the glomeruli, obviously have very great influence on that part of urine formation that depends on glomerular filtration as well as that dependent on tubular reabsorption in addition to such influences as are derived from changes in the walls of the glomerular capillaries and their coverings and in the cells lining the tubules

Unlike secretory glands the kidney is not directly under nerve control in the sense of there being true secretory nerves However the kidney has an adequate vasomotor nerve supply the splanchnic nerves bringing numerous vasoconstrictor and some vasodilator fibers and these profoundly alter the intrarenal circulation and in this way influence the excretion of urine In this sense there is a very definite neuroregulatory mechanism although it is an indirect one Finally, the kidney is unlike a secretory gland in that essentially it eliminates and does not form the constituents of its output except ammonia and hippuric acid, the latter an unimportant constituent of human urine Although the human kidney does not form substances to any great extent except ammonia it changes greatly the proportions of the constituents as they appear in the urine in contrast to their amount in the blood and in doing this the kidney carries on much work of great import to the organism in the maintenance of equilibrium of the constituents of body fluids and in ridding the body of end products of metabolism

Just how the kidney does its work has long been a topic of discussion and various theories have been suggested in explanation Cushny[10] in an admirable critical resume of renal function has advanced what he calls the 'modern theory" of renal activity which seems best to meet the known conditions of renal function According to this theory blood pressure in the glomerulus with its structure providing a filtration membrane causes filtration from the blood plasma of the constituents of the urine while active reabsorption in the tubules determines the final composition of the urine Filtration in the glomerulus is almost purely physical, absorption in the tubules depends on vital activity of the epithelium, selective absorption of numerous constituents in glomerular urine takes place in the tubules The other generally accepted theory differs only in making the action of the tubules actively excretory or secretory rather than absorptive Cushny himself makes no claim that his modern theory ' has been proved, but a critical demonstration of the correctness of the essentials of Cushny's views appears to have been made by Richards and his pupils[4 11 12] in their very ingenious experiments in which they quantitated in the frog the constituents of the fluid in

ar from constant Both amount and concentration vary from hour to hour so hat considerable periodic change in both is the normal condition [0] This varia ion is increased by the normal human habits of eating and drinking Normally lay urine excretion considerably exceeds night excretion Departure from the e ormal variations both over short periods and by day as contrasted to night are nd cative of disturbed renal function and form the basis of various concentration tests of renal efficiency which have a considerable value in clinical medicine

A very important function of the kidney is elimination from the body of acids formed in metabolism thereby maintaining in equilibrium the proper reaction of the plasma that is at a point slightly more alkaline than distilled water In contrast to this reaction urine is slightly acid The reaction of the blood lies between the limits indicated by litmus and phenolphthalein and that of urine between phenolphthalein and methyl orange The work of the kidney consists in shifting the reaction from the limit indicated by phenolphthalein and litmus to those indicated by litmus and methyl orange Henderson and Palmer [1 ™] calculate that in this work the kidney may free the body of 60 to 70 c c of normal acid per day under pathological conditions far more is removed Urinary acidity must be due to a weakly disassociated acid and the hydrogen ion concentration of the urine corresponds to the range between NaH_2PO_4 and $NaHPO_4$ It seems very probable that the phosphates are responsible in great part for the reaction of the urine When diuresis increases urine flow the urine becomes less acid in reaction and when urine excretion is decreased the reaction becomes more acid Obviously the reaction of urine is influenced by diet and other ingesta and by body activity katabolism as well as by the amount of urine flow

In considering renal function there is perhaps too much tendency to regard the kidney as a purely excretory organ and to overlook the fact that although chiefly concerned in excretion its ultimate usefulness is the regulation and maintenance of a stable fluid medium in the body In this regulation the inorganic constituents play a large rôle A B MacCallum[23] in a very interesting address has stressed this function of the kidney and it is of interest to quote from part of his address

Enough has been said here to emphasize the view that behind the functions of the renal organ is a history which links up the human body with the far past with an age of the earth when its oceans contained only what would now be regarded as brackish water and the earliest type of vertebrate life was just beginning to appear as a marine form From the facts advanced it will be gathered also that the blood plasma so far as its inorganic salts are concerned is but a reproduction of the remotely ancient ocean and that it is an heirloom from the life in

that immortal sea
Which brought us thither

TABLE I

	67 liters plasma contain		62 liters filtrate contain in all	61 liters reabsorbed fluid contain		1 liter urine contains	
	Per cent	Total		Per cent	Total	Per cent.	Total
Water	92	62 l	62 l		61 l	95	950 cc
Colloids	8	5 360 gm					
Dextrose	1 1	67 gm	67 gm	0.11	67 gm		
Uric acid	0.002	1.3 gm	1.3 gm	0.0013	0.8 gm	0.05	0.5 gm
Sodium	0.3	200 gm	200 gm	0.32	196 gm	0.35	3.5 gm
Potassium	0.02	13.3 gm	13.3 gm	0.019	11.8 gm	0.15	1.5 gm
Chloride	0.37	248 gm	248 gm	0.40	242 gm	0.6	6.0 gm
Urea	0.03	20 gm	0 gm			2.0	2.0 gm
Sulphate	0.003	1.8 gm	1.8 gm			0.18	1.8 gm

are not reabsorbed exert osmotic pressure and so influence reabsorption and these two differently acting groups have a large influence on the composition of the urine and, what is far more important on the resultant composition of the blood and body fluids Absorption is an active vital process although, of course greatly influenced by the physical and chemical properties and rate of flow of the fluid in the tubules and by variations in the blood flowing through the kidney

Blood supply to the kidney is a very great factor in determining renal function Richards and his associates[4, 19] and other investigators have shown the great importance of variations in renal blood pressure in determining urine flow The kidney differs from other secretory glands in its very close relation to the general circulation and its quick response to changes in blood pressure

Although the blood supply is such an important factor in renal function another paramount influence in determining the amount and composition of the urine is the chemical composition of the blood plasma What is filtered out in the glomerulus depends in large measure on what is contained in the blood coming to the glomerulus Tubular absorption returns to the plasma needed substances, threshold substances There is an optimal condition of solution for these and until this is reached absorption from the tubules takes place According to Cushny[10] this is an important determining factor in the final constitution of the urine As already pointed out colloid concentration in the glomerular capillaries exerts an osmotic tension which as colloids increase or decrease reversely affects filtration Many of these effects are dependent on physical conditions but in addition vital cell activity must play a part in tubules possibly in glomeruli

Under constant conditions of fluid and food intake hourly urine excretion is

no wise a sign of any actual kidney disease On the other hand if persistently present or repeatedly occurring it should be regarded as a definite sign of some disease of *unknown import to the individual until its nature has been determined* thoroughly All those who have done experimental work with the kidney realize how readily albuminuria develops after slight manipulation of the kidney or transitory changes in circulation and just as quickly disappears Severe exercise produces albuminuria in obviously sound kidneys in sound individuals Orthostatic albuminuria discussed on a later page needs recognition it hardly is a disease Slight irritants of a wide range of kind cause the same thing Febrile diseases in general usually are accompanied by it So it follows that when albuminuria is found it is a matter of importance to find out whether its presence can be explained by some simple cause in the groups just cited or whether with albuminuria the patient shows any other signs of organic renal damage Persisting or recurring albuminuria not orthostatic in nature particularly with casts or blood cells in the urine especially if the patient shows edema or circulatory disturbance with few exceptions means some form of Bright s disease whose importance to the individual depends on its subsequent course Such findings always merit the most careful study of the patient and considerable caution as to his activity It does not follow however that individuals found to have albumin and casts in one or several examinations necessarily have Bright s disease or have any greater probability of developing a subsequent Bright s disease than individuals never known to have shown these urinary changes

In the evaluation of the significance of albuminuria it is important to make a study of the conditions under which urine is being formed and excreted in relation to the position of the patient in other words to recognize from appropriate *methods of study whether the albuminuria is orthostatic or not* This is discussed in the subsequent section headed Orthostatic Albuminuria

Since albumin is not the only protein although the chief one that appears in the urine the term proteinuria is preferable to albuminuria However as albuminuria has had a very long and general usage in clinical medicine it will be continued to be used in this discussion of Bright s disease with the understanding that it means protein of the several forms that occur in the urine not just albumin Albuminuria in this sense is synonymous with proteinuria In most instances of albuminuria actually albumin constitutes a very large part of the protein appearing in the urine with the globulins making up but a small part [4]

Lee[5] found that nearly 5 per cent of 5 000 apparently healthy college men showed albumin in the urine as a definite ring with the nitric acid test for the most part without casts Following up these men they developed no signs of Bright s disease MacLean [6] got the same percentage of albuminuria in 50 000 *soldiers under military training and following these soldiers into active war service* he found that of the 132 subsequently developing Bright s disease *only* 17

not indeed in the Wordsworthian sense but in the literal one for the sea is the original home of all life on the globe and gave our blood and, accordingly, the tissues of our bodies, a character that long ages have not effaced and will not efface

The enormously long period during which the blood plasma has been simulating paleooceanic conditions in the concentration of its salts and in the ratios of the sodium potassium calcium and magnesium it contains emphasizes the importance in one respect of the organ which has maintained through the long ages of vertebrate history this concentration and these ratios, practically unchanged

'This organ is the kidney There is in invertebrates no structure with a similar function or with a function even distantly approaching that of the vertebrate kidney It is this organ that has made a fundamental difference between the vertebrate and the invertebrate not only in the struggle for existence but also in the capacity to evolve higher forms of animal life This function of the kidney is fundamental and is more ancient than that of excreting the waste products of the tissues of the body

In the long ages the kidney has thus performed a function which for constance and unvarying regularity is unrivalled in the world of life This constancy this unvarying regularity contrasts strikingly with the variation in function which the other organs have undergone and indicates how basic the kidney is in the vertebrate system and why it takes precedence in the body as a vertebrate organ par excellence'

PROTEIN IN URINE (Albuminuria)

Protein (albumin) in the urine (proteinuria or albuminuria) as determined by satisfactory clinical tests in a urine not concentrated by very great restriction of fluid intake always is an abnormality but this protein may indicate only a disturbance of renal function brought about in other ways than by what is to be regarded as a pathological lesion of the kidney, in other words it may not point to a diseased condition However, if great concentration of the urine is brought about then albumin is found by clinical tests and is to be regarded as a normal phenomenon[30,31] Clinical tests to be of practical usefulness should not be too delicate In all urine there is a small amount of protein material, a test so delicate as to detect this would be of no clinical usefulness consequently for use in the clinic the HNO_3 test and the heat acetic acid test, by reason of simplicity cheapness and degree of delicacy remain the preferable ones Of course numerous other ones are available

The presence in the urine of portein, a condition usually called albuminuria may indicate some trivial departure from normal function and if transitory be in

Dock s[32] observations and those of Canat and Wooley[32] in his laboratory give additional evidence of tubular reabsorption of albumin They could demonstrate in cells of the tubules of the rat s kidney particles of albumin stained with Evan s blue or trypan blue which had been excreted through the glomerular membrane and by perfusing the kidneys of the rabbit with ice cold serum which paralyzes the tubule cells a method of study developed by Bickford and Winton[33] they could obtain a glomerular filtrate with albumin content of 15 to 2 mgm per 100 c c a concentration not present in the urine from kidneys not so perfused Gerard[34] also has shown that reabsorption and alteration in dispersion of colloid and particulate matter take place in tubular cells if these substances are introduced into the proximal end of a proximal convoluted tubule

These observations indicate that lesions in both glomeruli and tubules can play a part in the degree of observed protein in the urine In other words clinical albuminuria can be the result of glomerular lesions increasing protein passage of filtration or of tubular lesions decreasing protein absorption or of a combination of these two processes In view of this work no longer is it necessary to predicate glomerular lesions to explain every clinical albuminuria failure of tubular reabsorption can be a cause Furthermore it is possible for there to exist greater glomerular damage than is indicated by the degree of clinical albuminuria if and when tubules only slightly damaged actively reabsorb a considerable part of the protein that has leaked through the damaged glomerulus This will explain those cases of Bright s disease in which very extensive structural changes in the glomeruli are seen in the kidneys when during life albuminuria has been slight and also those cases in which the reverse has been true namely marked albuminuria with the finding of almost no demonstrable structural change in the glomeruli A better correlation of the pathological changes observed in the kidney after death with the intra vitam quantitative determinations of albuminuria now becomes possible

Nature of Protein in Urine

The source of the protein in the urine in very large part is plasma protein The various proteins present in the blood pass from the blood through the kidney into the urine under certain conditions mainly conditions that have damaged the glomerular membrane conditions present in Bright s disease This is caused *in the main by a process of differential filtration dependent upon the differing* sizes of the molecules of different proteins[31] and the degree of injury to the glomerular membrane A certain part of this protein does not reach the urine in soluble form but is precipitated within the kidney to form casts and possibly to make hyaline deposits in the kidney chiefly in and about the wall of the glomerular loops possibly also in cells lining the tubules Protein also is reab

per cent had shown albuminuria in the earlier examination at a time when there was no evidence of an actual Bright's disease It would seem that such finding of albuminuria in otherwise apparently healthy individuals should occasion no particular alarm

The view has been held generally in the past that in the normal kidney molecules as large as those of albumin globulin and fibrinogen do not pass or pass only in very small amounts from the capillaries of the glomeruli through the capillary *wall and its covering derived from the tubule into which the capillary loops* have been invaginated i e that the process of glomerular filtration holds back molecules of this magnitude, unless this filter has been damaged This view was based very largely on study of the kidney of amphibians[4] In other words the view was that more than a very small amount of protein in the urine indicates damage to the glomerular filtration membrane and that the amount roughly is proportionate to this damage because no reabsorption of this protein takes place in the tubule and no protein actually is excreted by the tubule That this amount in the urine may be increased by protein derived from the degeneration of cells lining the tubule or that possibly some may reach the lumen of the tubules by passage through the walls of the intertubular capillaries as occurs in an inflammatory exudation has been realized

More recently evidence has accumulated that a considerably larger amount of protein than formerly was accepted as normal passes normally through the glomerular membrane and that under normal conditions much of this is reabsorbed in the tubules to leave only in the urine that small amount which is regarded as normal for man[7] Different mammals vary with regard to these activities of glomerulus and tubule in relation to excretion and reabsorption of protein Some as the Slonaker strain of albino rats excrete a considerable amount of protein in their urine Under ordinary conditions this is of an order not dissimilar from that observed in many patients with Bright's disease This excretion after an interval of time can be increased either by increasing consumption of food protein or by decreasing the number of nephrons by removing part of the kidney [7] This seems to indicate that the rate of protein excretion increases after the amount of osmotic work *per gram of renal tissue or per nephron* has been increased According to Addis this is equivalent to saying that protein excretion can be altered by a factor that is effective with respect to the tubules not the glomeruli In mammalians Walker and Oliver [8, 9] have found a concentration of protein less than 30 mgm per 100 c c of glomerular fluid in only two out of six collections If in man similar glomerular excretion of protein occurred let us say 20 mgm per 100 c c in man's usual glomerular filtrate of 180 000 c c there would be 36 gm of protein but Addis had found using his special methods[30], that normal man's actual 24 hour excretion of protein in the urine was only 0 01 gm [31] This can be interpreted simply as indicating a considerable reabsorption of protein from the urine in the tubules

Dock's[32] observations and those of Canat and Wooley[33] in his laboratory give additional evidence of tubular reabsorption of albumin. They could demonstrate in cells of the tubules of the rat's kidney particles of albumin stained with Evan's blue or trypan blue which had been excreted through the glomerular membrane and by perfusing the kidneys of the rabbit with ice cold serum which paralyzes the tubule cells, a method of study developed by Bickford and Winton[33], they could obtain a glomerular filtrate with albumin content of 15 to 22 mgm. per 100 c.c., a concentration not present in the urine from kidneys not so perfused. Gerard[34] also has shown that reabsorption and alteration in dispersion of colloid and particulate matter take place in tubular cells if these substances are introduced into the proximal end of a proximal convoluted tubule.

These observations indicate that lesions in both glomeruli and tubules can play a part in the degree of observed protein in the urine. In other words clinical albuminuria can be the result of glomerular lesions increasing protein passage of filtration or of tubular lesions decreasing protein absorption or of a combination of these two processes. In view of this work no longer is it necessary to predicate glomerular lesions to explain every clinical albuminuria; failure of tubular reabsorption can be a cause. Furthermore it is possible for there to exist greater glomerular damage than is indicated by the degree of clinical albuminuria if and when tubules only slightly damaged actively reabsorb a considerable part of the protein that has leaked through the damaged glomerulus. This will explain those cases of Bright's disease in which very extensive structural changes in the glomeruli are seen in the kidneys when during life albuminuria has been slight, and also those cases in which the reverse has been true, namely marked albuminuria with the finding of almost no demonstrable structural change in the glomeruli. A better correlation of the pathological changes observed in the kidney after death with the intra vitam quantitative determinations of albuminuria now becomes possible.

Nature of Protein in Urine

The source of the protein in the urine in very large part is plasma protein. The various proteins present in the blood pass from the blood through the kidney into the urine under certain conditions, mainly conditions that have damaged the glomerular membrane, conditions present in Bright's disease. This is caused in the main by a process of differential filtration dependent upon the differing sizes of the molecules of different proteins[31] and the degree of injury to the glomerular membrane. A certain part of this protein does not reach the urine in soluble form but is precipitated within the kidney to form casts and possibly to make hyaline deposits in the kidney, chiefly in and about the wall of the glomerular loops, possibly also in cells lining the tubules. Protein also is reab-

sorbed in some degree in the tubules Degenerating cells of the tubules also can contribute some protein to the urine It is possible that some protein is excreted or filtered from the bood by way of the tubules The protein in the urine, con tributed as just outlined differs from the protein in the blood in certain aspects, in both places blood and urine, albumins and globulins are the chief components of the protein but the percentage composition of the several components of the protein moiety is not the same in each place[63–0] Furthermore in a reciprocal way this process of renal loss of protein progressively changes the composition of the plasma protein, and this change subsequently influences the composition of the urinary protein

As already pointed out the amount of protein in the urine depends on a bal ance between two processes glomerular filtration and tubularre absorption with certain other factors, already mentioned being contributory Even some excre tion of protein by the cells lining the tubules is claimed Somewhat against this, however is the statement that in fish toxic substances, which will cause albu minuria in those fish that have glomeruli in their kidneys, fail to cause albuminuria in the variety of fish that have aglomerular kidneys[71]

Urinary proteins with few exceptions are of the same structural composition as the proteins in normal blood plasma[63–70] The proportion of these several varieties of protein in the urine differs from that in the blood plasma[63–0], this difference depends mainly on variations in the size of molecule in each variety, those with smaller molecules more readily passing the damaged barrier of the glomeruli However there is evidence that in some cases of Bright s disease varieties of protein not in normal blood plasma appear there and that these in turn pass into the urine [2–60] Some even believe that a change may take place in a protein as it passes from the blood through the kidney into the urine The composition of plasma protein will be discussed later in this chapter in the section headed Blood Chemistry

If the protein in the urine of patients with Bright's disease is separated into albumin and globulin it will be found that in most of the patients albumin con stitutes the bulk of the protein but in some of them particularly in those with a large amount of protein in the urine the proportionate amount of globulins is considerably increased[63] In different cases of Bright s disease the percentage of albumin in the urinary protein has been found to vary from almost 100 per cent to such figures as 87 80 75 71 62 58 per cent to cite determinations in indi vidual cases[63] For an individual patient the total amount and the proportion of the various proteins in the urine varies from time to time[63] (Figs 1 2 3 and 4) With ordinary or low protein diet albumin usually makes up most of the urinary protein, while on high protein diet although the albumin increases in absolute amount the other proteins chiefly globulins increase in proportion and the al bumin then constitutes a smaller proportion of the urinary protein, urinary protein

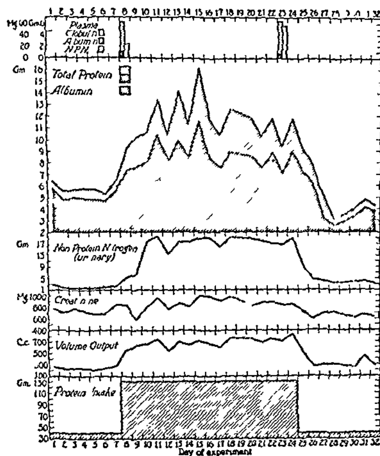


Fig 1 — Elimination of urinary protein in patient with nephrotic syndrome as influenced by level of protein intake (from Berglund Scriver and Medes)

now approaches more nearly to the composition of plasma protein Fever similarly will increase total urinary protein and decrease its percentage of albumin

In a general sense as albumin is such an important often the dominant part of the protein found in the urine this passage into the urine of protein leads to a progressive decrease in the albumin moiety of plasma protein with or without more often with a decrease in total plasma protein[80] As will appear later in a discussion of Blood Chemistry and of Edema this is of much importance in the body economy because the albumin molecules are smaller and exert a greater osmotic pressure than do the globulin molecules this is a causal factor in the development of edema

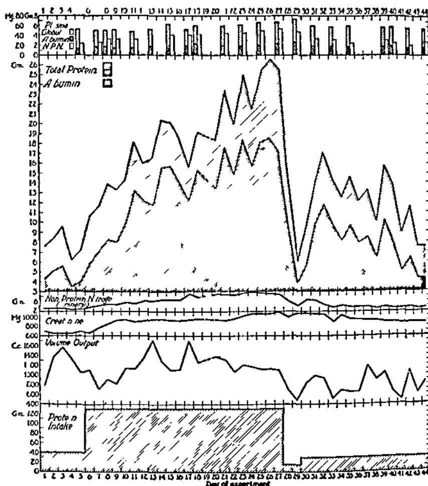


Fig 2 — Elimination of urinary protein in patient with nephrosis syndrome as influenced by level of protein intake (from Berglund Scriver and Medes[61])

Orthostatic Albuminuria

There is a fairly common definite type of albuminuria so-called orthostatic albuminuria which does not seem to have any serious significance Other terms that have been suggested for this condition are lordotic cyclic intermittent variable, orthotic juvenile or adolescent albuminuria The chief characteristic is the rapid appearance of albumin in considerable amount in the urine after the patient has been in an upright position and its disappearance from specimens passed following a prone position In other words urine formed, when the patient is upright contains albumin and, when flat contains none Often the albumin is

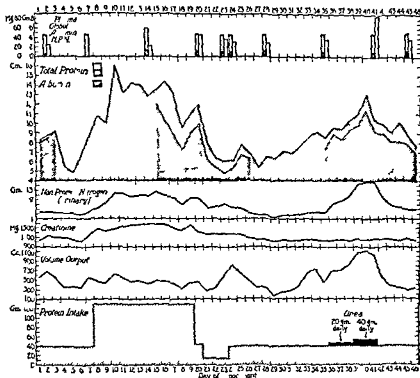


Fig 3 — Elimination of urinary protein in patient with nephrosis syndrome as influenced by level of protein intake and by ingestion of urea (from Berglund Scriver and Medes[65])

more abundant in the first hour or two of the upright position than later on Active moving about or eating occasionally may decrease the albuminuria or even cause its disappearance On the other hand exercise may increase the albuminuria or it may follow vigorous exercise when absent under other conditions Strenuous exercise persisted in as a rule causes albuminuria as seen in many marathon runners With the albumin a few hyaline casts and even cells may appear in the urine not concentrated by the method of Addis although ordinarily this does not happen Rarely red cells appear

Jehle[35 36] has given one of the best discussions of orthostatic albuminuria He believes that in many of these individuals it is not the upright position but an excessive lordosis that determines the albuminuria The patient may stand with the lordosis corrected and his urine show no albuminuria or he may lie flat with a lordosis made by a firm pillow under his lumbar spine and show albuminuria Others while accepting Jehle s other ideas as to orthostatic albuminuria do not

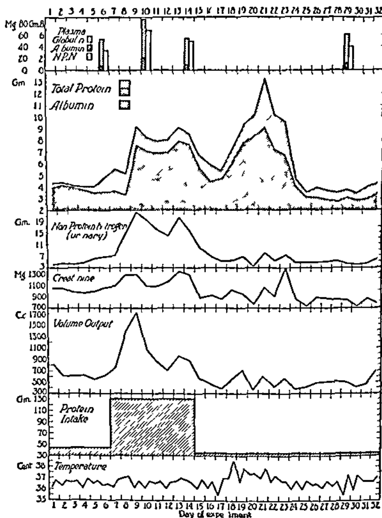


FIG 4 — Elimination of urinary protein in patient with nephrosis syndrome as influenced by protein intake and by fever (from Berglund Scriver and Medes [?])

concur in his belief in the importance of lordosis as the causative factor Still others think that usually there is an abnormal permeability of the kidney and so in a sense some underlying pathological element (Russell[37])

Orthostatic albuminuria occurs in youth most often between about nine years of age and most frequently the time of puberty and particularly in thin types that have increased rapidly in height In this group it is a quite frequent finding the percentage varying with the delicacy of the tests used Perhaps it is best to accept as cases of orthostatic albuminuria only those with a definite ring of

albumin by the nitric acid test in urine passed in the upright position Such findings usually disappear in early adult age In some there are no associated symptoms and some are of unusually fine health as in candidates for West Point otherwise free from other defects but many of these individuals are easily fatigued *often pale neurasthenic with frequent headaches or pain in the back* Palpitation, cardiac arrhythmia and vasomotor instability are not infrequent These various symptoms probably are the accompaniment of the habitus of the patient rather than the result of any disturbance in renal function

An interesting form of orthostatic albuminuria is that which develops during convalescence from acute Bright s disease and which may persist for long periods of time sometimes being permanent Derow s observations on this are important[347 349] As the urine clears of the abnormal features which have been present and reaches the stage when albuminuria is the chief abnormality if properly tested it will be found that an orthostatic element in the albuminuria has appeared although still there is slight albuminuria in urine passed under conditions to eliminate the factor of orthostasis Gradually this changes by the disappearance of albumin from the urine which is passed in the reclining position but its continued persistence in urine passed with the patient out of bed and active Such orthostatic albuminuria appears to do the patient no harm, he is symptomless Furthermore it seems that its presence after acute Bright s disease is not an indication of a latency of process which may be expected later to develop into a progressing chronic Bright s disease In other words it seems to be of no bad prognostic omen Its recognition by appropriate tests seems of much importance in the follow up and evaluation of the condition of patients who have had acute Bright s disease This is discussed further in the section on Prognosis in the discussion of acute Bright s disease in Part II Unlike orthostatic albuminuria without antecedent acute Bright s disease this type is not all predominatingly in tall thin adolescents who are growing or have grown rapidly but occurs at any age and in any habitus of patient

Orthostatic albuminuria is diagnosed from the results of certain tests Suggestive evidence of it exists when the patient s urine passed immediately after arising in the morning contains very little or no albumin by the usual tests while that passed one half to two hours later contains a definitely increased amount

According to Jehle[35 36] confirmation is obtained from the following observations The patient is put to bed a half hour later the bladder is emptied the patient is continued in bed until a second specimen can be passed It is important that the patient lie with his body flat he may lie either on his side or back The patient then gets up and stands moving about to a moderate extent When the patient can void a urine specimen is obtained and later a second specimen The period in bed can be repeated if one wishes or the patient may

stand with one foot elevated on a chair, a position that will straighten the back out from any lordotic curve

Derow[349] has planned an excellent method for the study of ambulatory patients in whose urine any albumin has been detected It is as follows

(The following printed form was given to each patient before the start of each study)

Orthostatic Albuminuria Test

Before starting this test secure 6 to 10 clean dry 4 ounce bottles Female patients should use clean dry wide mouthed jars

Paste a blank label on each bottle Number each bottle consecutively beginning with 1 Write the hour and date of voiding on the label as each bottle is consecutively used

1 One hour after going to bed night empty your bladder while still in bed using a bedpan or bottle have someone else discard this urine

2 When you awaken morning while still in bed pass your urine into bottle No 1

3 Get out of bed and kneel on the floor with your head erect and your shoulders thrown back for 10 minutes by the clock Then while still kneeling pass your urine at the end of this time into bottle No 2

4 Do not drink any liquids (water coffee tea soups milk and so forth) all day

5 You may now have your breakfast and go about your daily routine

6 From now on whenever you have to pass your urine do so into one of the lab l d bottles or jars and write the date and hour of voiding on the label

7 The last urine saved will be that which is passed morning

8 Please bring all the bottles properly labeled to the clinic (or office) on morning

Each sample of urine was tested for albumin by the Heller ring method as follows Approximately 2 c c of concentrated nitric acid was poured into a small wineglass and the urine was filtered so that the filtrate overlay the acid After an interval of one minute the line of contact of the urine and acid was carefully observed for the presence of a white ring indicating the presence of albumin A ring seen only against a black background was considered a slightest possible trace (<+) a ring observed against any background was considered a very slight trace (+) a ring seen against any background and just visible from above was considered a slight trace (++), a ring which was opaque from above was considered a trace (+++) and a very flocculent ring opaque from above was considered a large trace (++++)

In the performance of the Heller ring test for albumin it is important to use clean glassware good filter paper (Whatman s No 1) and a good light source Cloudy and alkaline urines should be centrifuged before they are filtered

The specific gravity and reaction to litmus of each sample of urine were also determined The sediment obtained by centrifuging the sample passed in the clinic or office was studied for formed elements His findings in the group with postural albuminuria fell into five categories

Type 1 Albumin was not found in the urine collected at the conclusion of the period of recumbency there was marked albuminuria at the end of a ten

TABLE II

Time of Occurrence of Albuminuria in Ambulatory Patients

Kind of Albuminuria	After Nocturnal Recumbency	After Ten Minute Lordosis	Ambulatory State			
			Morning	Noon	After noon	Evening
None	o	o	o	o	o	o
Constant			+	+	+	+
Postural						
Type 1	o	+	+	o	o	o
Type 2	o	+	+	+	+	o
Type 3	o	o	+	+	o	o
Type 4	o	o	+	+	+	o
Type 5	o	o	o	o	+	+

+ = albumin present o = albumin absent

minute period of exaggerated lordosis Albuminuria disappeared by midday

Type 2 Albumin was not found in the urine collected at the conclusion of the period of recumbency there was marked albuminuria at the end of the ten minute period of exaggerated lordosis Albuminuria continued throughout the day until evening

Type 3 Albumin was not found in the urine voided at the end of recumbency and after lordosis It appeared promptly after the upright position was assumed and continued until midday but was absent in the afternoon and evening

Type 4 Albumin was not present in the urine voided during recumbency and after lordosis but appeared in the urine voided after the upright position was assumed it continued to appear until evening

Type 5 Albumin was present in the urine only in the afternoon and evening

Types 2 and 5 of postural albuminuria were most frequently found The type usually varied from time to time in a given patient Occasionally in a patient with postural albuminuria albumin was absent from the urine during a given test period only to recur in subsequent studies

His conclusions from this study were as follows

A method of study of albuminuria in ambulatory patients without symptoms is presented It consists of the study of the concentration of albumin in consecutive samples of urine voided over a period of twenty eight to thirty four hours under fixed test conditions

Such albuminuria may be constant postural or occasional

Constant albuminuria is found in all patients with overt chronic nephritis

Postural albuminuria is present in patients without evidence of organic renal disease A small number of patients recovering from an initial attack of overt nephritis show postural albuminuria for several months before the urine becomes free of albumin

Constant albuminuria even in the absence of any history of an antecedent overt episode and of any other findings is indicative of organic renal disease

Patients with primary arterial hypertension may show no albuminuria or may show occasional albuminuria or constant albuminuria, but never postural albuminuria

The urine voided in the midmorning after the patient has been up and about will show albumin more often than any other voided during the twenty four hour period

If the patient has a true orthostatic albuminuria the specimens passed when lying down or when standing with one foot elevated on a chair will show no albumin while the others will contain albumin often in considerable amount The first urine passed after lying down may contain some albumin in large part because some urine formed in the upright position and containing albumin remains in the bladder ureters and renal pelves and this mingles with urine subsequently excreted that is albumin free In addition in some cases it takes a little time after change of position for the albumin to cease appearing in excreted urine

Jehle s[35 36] explanation of this type of albuminuria is that it results from the lordosis and consequently in carrying out the tests one must make sure that the change of position actually allows or prevents the lordosis as the case may be One may stand in such a way as to fail to have the lordosis that is customarily present and so fail to have albuminuria or one may lie in bed and by the position assumed maintain lordosis and so have the albuminuria persist According to Jehle the lordosis causes renal congestion by hindering venous outflow from the kidney and hence the albuminuria

When the tests give clear-cut results and there is nothing in the history of physical examination to suggest an actual Bright s disease the diagnosis is definite If a few casts and cells accompany the albuminuria the possibility of a coincident slight Bright's disease is increased There are patients in whom change of position merely decreases or increases albumin in the urine and some albumin persists in the urine in any position of the body These cases appear to belong to the

same category but there is a greater possibility here of an element of Bright's disease When genuine hyaline casts are more than rare and granular casts are present, however my feeling is that such patients have some degree of true Bright's disease as well as an orthostatic albuminuria An orthostatic element in mild Bright's disease is fairly common here a careful study of the casts and cells is of great usefulness in making a correct diagnosis In some of these patients chronic infection of the tonsils teeth sinuses etc may be found and their eradication may clear up the urinary findings Its persistence into the stage of healing in a patient who has had an active Bright's disease already has been referred to

There are occasional variations from the type orthostatic albuminuria described in the preceding paragraph Older individuals may show the same type of albuminuria as just described although it is true that the greatest frequency lies in the *earlier periods of life* *There is a rare occurrence of albuminuria in the* reclining position to disappear in the erect posture clinostatic type (Rolleston[38]) An enlarged spleen in certain positions of the body may depress the left kidney and thus lead to albuminuria such as occurs with lordosis Sometimes the albuminuria seems to be merely the result of an excessive ingestion of some form of protein such as its appearance when much raw or slightly cooked egg albumin is taken Cystoscopic examination has shown that the albuminuria may be unilateral[39] or bilateral Sonne claimed it was always left sided i e came from the left kidney but others have found it on the right side Left sided albuminuria has been explained by the Riesers[40] as due to pressure on the left renal vein by compression between the aorta and mesenteric artery in the upright position by the visceroptotic pull of the mesocolon Ryland[41 42] found decreased diodrast excretion from the left kidney in upright position Vigorous palpation of the kidney when used in some patients also may cause albuminuria

Erlanger and Hooker[43 44] have shown in a patient very carefully studied by them a decrease in pulse pressure in the upright position largely as the result of a rise in diastolic blood pressure and give this as the cause of orthostatic albuminuria When this patient was suspended in an upright position in water these phenomena did not appear Post and Thomas[45] found that neutralization or mild alkalinization of the urine by various alkaline salts or from a diet rich in vegetables and fruits would cause the albumin no longer to be demonstrated by the usual tests

From all of this it would seem that several factors play a part in causing orthostatic albuminuria and that in carefully studied cases a fairly wide variation in findings may be encountered but almost all agree that the disturbance in renal function is slight often inconstant and not indicative of any organic lesion of the kidney

The majority of observers believe that as patients grow older orthostatic

albuminuria will disappear and that these individuals have no increased probability of a subsequent Bright's disease To them, if it is to be considered a disease its prognosis is perfect Perhaps it is better to regard it merely as a disturbance practically within the range of normal physiological function and of good prognosis We would agree with this view Others however, believe it is an undesirable abnormality if not a true disease, and that prognosis is doubtful since sometimes the condition advances into a true Bright's disease At any rate it would seem desirable to treat these individuals with orthostatic albuminuria by postural correction and good general hygiene to prevent the condition from persisting if it is merely a result of posture It is questionable if anything is gained by alkalinization of the urine as suggested by Post and Thomas[45] If orthostatic albuminuria represents an actual although slight degree of Bright's disease avoidance as far as possible of infections and their prompt treatment, if they occur certainly is indicated However, undue restrictions as to diet and activity are to be avoided for after all these patients rarely progress into any serious renal condition It seems wisest to the author to regard these individuals as not sick and not to burden them with advice beyond that of sane hygiene suited to all An increasing belief that orthostatic albuminuria does not point to a diseased kidney is indicated by admissions to West Point Military Academy of young men showing it

Albuminuria of Passive Congestion

The importance of calling attention separately to the albuminuria of passive congestion lies in the frequency with which patients are diagnosed as having Bright's disease when the urinary findings merely result from the circulatory changes in the kidney caused by a diseased heart Especially in those edematous cardiac patients with a regular not rapid pulse rate is this error likely to be made A very considerable albuminuria with hyaline and granular casts and a few red blood cells in a urine of decreased amount and normal or increased specific gravity may be due to passive congestion of the kidney and with effective treatment of the cardiac condition be replaced by normal or almost normal urine In hypertensive patients an increase in albumin and casts without or with red blood cells often is an early sign of developing circulatory disturbance The kidneys of edematous patients with passive congestion usually respond to digitalis or to diuretics following digitalis with a prompt and marked increase in urine output, indicating a good functional efficiency in the kidneys which is less or lacking when these same urinary changes are the result of Bright's disease In this group of patients it is the evidence of cardiac enlargement and other cardiac abnormalities and the response to treatment rather than the urinary changes themselves which are important in the recognition of the cause of the urinary disturbances

The state of the urine after circulatory decompensation has been restored is important in determining the presence or absence of Bright's disease. Unless the circulatory cause of the urinary changes is recognized, the wrong treatment is given, and the patients do not improve as they should; they should be treated as cardiac rather than renal patients. The diagnosis of cardiorenal disease is an unfortunate one for them as perpetuating the idea that the renal element is other than secondary to the cardiac lesion.

Febrile Albuminuria

Fever, if prolonged, whatever its cause, almost always is accompanied by albuminuria. Probably this is more an effect of toxic substances that are being eliminated than of the fever. However, Wolty[16] found albuminuria in 77 per cent of 40 patients whose body temperature was elevated to 105° to 106° F for 4 to 6 hours by the Kettering hypertherm, showing that the cause is not necessarily a toxic substance of infectious origin. Febrile albuminuria usually is slight in degree, and casts and cells are infrequent if the patients have a large fluid intake with a correspondingly increased urine output. In some patients with febrile albuminuria O'Hare finds loosely knit casts with medium sized blackish granules to be quite numerous. If albumin is considerable in amount and casts, especially coarsely granular casts, are numerous, it is safer to regard this evidence as indicative of an actual acute Bright's disease of mild grade. If red blood cells are numerous, this probability of Bright's disease is enhanced. Ordinarily these findings in the urine disappear with subsidence of the fever. When they persist, and particularly when they appear during convalescence, they point to a complicating or secondary Bright's disease. In patients dying from acute infectious diseases albumin and casts may be very abundant in the urine near the end of life, and yet the kidneys show microscopically very little evidence of any lesion of a nature to be interpreted as Bright's disease (unpublished observations of the author), so that it is unsafe to make a diagnosis of acute Bright's disease from changes in the urine excreted in febrile conditions shortly before death.

Casts and Cells in the Urine

Like albumin, casts and cells in the urine, not greatly concentrated, indicate a disturbance in the kidney; if great concentration of urine is brought about, then casts and cells will be found up to a certain number without indicating any renal abnormality, as Addis showed in his work.[30, 31] It must be recognized that very slight changes in the kidney may cause the appearance of a few casts and cells, and that with the high speed centrifuge the number of individuals showing casts has been greatly enhanced as contrasted to older statements based on gravity or

blowing it out of this pipette One drop of this is placed in a blood counting chamber and the casts and other formed elements are counted under the microscope using a high dry lens From these counts the number of casts and formed elements in the 12 hour night urine are calculated

In Addis counts red blood cells from 0 to 425 000 with average of 65 760, leucocytes and epithelial cells from 32,400 to 1 000 000 with average of 322,550 and hyaline casts from 0 to 4,270 with average of 1,040 are regarded as normal values for such concentrated night urine These values translated to the usual method of examining an unconcentrated urine centrifuged at a rapid rate in a high power centrifuge mean that a few red blood cells, 3 to 6 per high power field under the microscope, slightly more leucocytes and epithelial cells and a rare hyaline cast are to be considered normal findings, while larger numbers indicate some pathological lesion of the kidney In older patients an occasional hyaline cast scarcely can be considered pathological In women more cells may be expected under nonpathological conditions than are normal for men unless urine specimens are obtained by catheterizing the bladder

The examination of a single specimen of urine may give information of great value but it is far safer to defer deductions until several have been studied Here as in many other methods of examination it is better to base opinions on repeated examinations covering a considerable number of days

One of the most useful services of examinations for casts and cells lies in its aid to prognosis so long as there are evidences of considerable activity i e numerous and a variety of casts and cells there is the possibility of very striking improvement Signs of chronicity in the sediment i e , a persistence in but not very numerous casts and cells when there are other evidences of extensive involvement suggest a poor prognosis as to marked improvement

Blood Chemistry

As the kidney is an excretory organ disturbance of its function will disturb the constituents of the body that leave it by the kidney Since these reach the kidney by the blood stream disturbed kidney function should cause changes in the amounts of the various substances present in the blood unless quickly there is a compensation from the body fluids and tissues Actually we do find change in the blood composition when kidney function is disturbed Improvements in chemical technique many of which were made by Folin and Van Slyke and their pupils have made possible an accurate quantitative determination of numerous substances in small quantities of blood and hence we have been able in the clinic to make oft repeated estimates of them and follow changes that occur during the process of disease in our patients Consequently there has grown up a very considerable knowledge of what we term the blood chemistry of Bright s disease

It is to be remembered that Bright s disease is not a disease of the kidneys alone but a generalized process with as a rule definite disturbances in the circulatory mechanism and changes in body metabolism All contribute to the changes found in the blood There may be accumulation in the blood of substances the result of katabolism and of retention These may be such substances as normally are being excreted and so present in the blood in smaller quantities during normal renal function There is some evidence too that substances not normally present may appear (Foster[4] and others) Slight changes may disturb seriously that normal equilibrium of substances in the body fluids which is so essential for the normal function of body tissues Changes in equilibrium may lead to acidosis or alkalosis and become a complication in terminal stages of renal lesions Other changes in equilibrium may be equally important Homeostasis a term introduced by Cannon is very essential to normal body function and even slight disturbance of it may lead to serious consequences Our present knowledge is most complete in regard to retention products but physical chemistry however is rapidly laying the foundations for better understanding of variations in equilibria of substances in osmotic tension surface tension etc and their import in diseased conditions

Non protein Nitrogen

So far we have learned much about the changes in the non protein nitrogen elements of the blood in Bright s disease The total non protein nitrogen in the blood is made up to several end products or stages in the metabolism of exogenous or endogenous protein It averages between 15 and 40 mgm per 100 c c of blood

in normal men These non protein nitrogen substances are urea, uric acid, creatinin, amino acids and the somewhat questionable "rest nitrogen" or the fraction left after the other fractions have been determined

Urea Nitrogen —Of these non protein nitrogen substances, knowledge of the changes in urea has been most generally useful in our study of Bright's disease more useful even than of the total non protein nitrogen itself Some, however, prefer to determine the total non protein nitrogen, and on the whole the significance of the two is much the same The usefulness of blood urea determinations depends on the fact that its determination has been fairly easy and accurate that it represents one substance about whose derivation we are reasonably sure, that it leaves the body largely, but not entirely by way of the kidney and that it is such a diffusible compound that its content in body fluids everywhere remains remarkably even

We know that the urea in the blood is a product largely of the protein taken in the diet together with additions from the breakdown of endogenous tissue protein As such therefore its level in the blood stream is determined largely by three factors protein intake the degree of renal insufficiency and the amount of tissue protein katabolism Ordinarily this last factor is a relatively unimportant one When however the patient is in uremia and is vomiting or unable to take food it plays a very prominent part At such times this explains the very rapid rise in the blood urea which often is observed If the patient becomes oliguric or anuric the level of the urea in the blood rises rapidly due to the causes mentioned above and also to the fact that the kidney requires considerable water for the excretion of this substance (Pepper [0]) A high protein intake with moderate renal insufficiency may yield quite high values for blood urea nitrogen while with a low protein intake the same patient will show a much reduced or almost normal blood urea nitrogen

In the normal individual the urea nitrogen makes up about 40 to 50 per cent of the non protein nitrogen in the blood In renal insufficiency, however, this percentage may rise rapidly to 70 to 80 per cent Normally the urea nitrogen content of the blood taken in a fasting state i e before breakfast is from 8 to 15 *mgm per 100 c c Mosenthal and Hiller*[51] *have shown that this ratio* remains fairly constant in inactive chronic Bright s disease irrespective of the level of the non protein nitrogen In this way in some patients there will be an increased blood urea nitrogen when total non protein nitrogen may still be within normal bounds although at a high normal level

Uric Acid —The amount of uric acid in the blood according to an earlier view as expressed by Myers Bauman [3] and their associates serves as a particularly valuable index of renal function since they thought that it was excreted by the kidney in such a way that slight disturbances of renal activity caused its

increase in the blood beyond its normal value However numerous observers since then have thrown doubt on the idea that its increase is an early and satisfactory index of renal insufficiency Under normal conditions it is one component of the non protein nitrogen of the blood but not a large one 2 to 4 5 mgm per 100 c c Methods for its determination have changed often with variation in what is regarded as normal values so that the method used needs to be taken into account in reading different papers on the subject With present methods determination of serum or plasma values seem more consistent than those of whole blood In serious Bright s disease increase often is very considerable slighter increases occur in patients obviously not suffering from Bright s disease In our experience at the Peter Bent Brigham Hospital its increase has not always antedated increase in blood urea nitrogen Sometimes its value has remained normal with a definitely increased blood urea nitrogen or after moderate increase it has remained stationary while other forms of non protein nitrogen were increasing With such discrepancies its estimation at present seems of relatively little practical value in the study of patients with Bright s disease However it is of great importance in the study of gout although in gout it is not an index of renal insufficiency [4]

Creatinin — Creatinin being almost solely a product of endogenous protein metabolism is practically unaffected by the diet except insofar as this influences the breakdown of tissue protein In normal blood its value is 1 to 2 mgm per 100 c c In renal insufficiency it often increases [5,56] but not always in proportion to urea nitrogen the latter may be high with normal value of creatinin In chronic Bright s disease when it reaches 5 or more mgm per 100 c c of blood prognosis is grave but death may be delayed for as long as 3 years as we have seen at the Peter Bent Brigham Hospital[57] In acute Bright s disease with anuria or marked oliguria such high values may occur and yet later return to normal as the acute process subsides as in a patient in which we saw as high a value as 19 mgm return in 45 days to a level of 1 6 mgm per 100 c c

Amino Acids — Amino acids so important in the process of protein utilization in the body are taken out of the blood stream very rapidly by the body tissues so that only relatively small amounts 5 to 8 mgm per 100 c c are in the blood under normal conditions [9] There are more than a score of amino acid in the body but there is not much data on the presence of these individual amino acids in the blood under varying conditions It is only in advanced Bright s disease with marked nitrogen retention that considerable increase in amino acid nitrogen occurs and even then high values are infrequent unless there is combined with the renal insufficiency a considerable hepatic insufficiency [1,8,6] Experimentally in the dog if the liver has been removed blood urea decreases and injected amino acids remain at a high level in the blood in the absence of an

increase in blood urea If the kidneys are removed from an animal, a marked rise in blood urea follows but this does not occur after the simultaneous removal of kidneys and liver (Mann and associates [1]) The ability of the kidney to remove the amino groups contained in amino acids is of considerable significance in the problem of maintaining acid base balance in the body, inasmuch as ammonia formed from amino acids by the kidney cells acts to conserve to the body other base needed to keep the pH of body fluids and tissues within normal range Recently Van Slyke and his associates[6] have shown that glutamine plays a very important role in the formation of ammonia by the kidney Urea, as previously believed is not the source of the ammonia formed by the kidney according to Van Slyke and associates[6] Renal disease inhibits ammonia formation by the kidney and is a contributory factor to the development of acidosis in severe Bright's disease

Ammonia Nitrogen —Ammonia nitrogen runs between 0 1 to 0 2 mgm per 100 c c of blood in normal people This is not increased but rather decreased by the renal insufficiency of Bright's disease as pointed out in the previous paragraph Its formation in the kidney now is believed to be from the amino acid, glutamine not from urea as previously believed

Rest Nitrogen —When these various forms of non protein nitrogen, separately determined are added up and compared with the amount of total non protein nitrogen determined in the blood there is a discrepancy, this excess nitrogen is called ' rest residual or undetermined nitrogen and will amount to 5 to 18 mgm per 100 c c of blood This according to some observers is made up of the nitrogen of hippuric acid, nucleotides and histones In marked renal insufficiency this form of non protein nitrogen may be increased much in proportion to the determinable forms Some believe that under these circumstances part of the rest nitrogen represents nitrogenous substances not normally present and possibly more toxic than urea uric acid creatinin and amino acids normally present in the blood

Plasma Protein

The composition of plasma protein and its total amount as well as the amount of its several components is of great importance in the body economy and function[62 7] Since in Bright's disease departures from these normals occur, a knowledge of them has become of great importance in an understanding of the disease Because the renal lesions of Bright's disease indirectly cause changes in the qualitative and quantitative composition of plasma protein plasma protein values indicate changes that are taking place in renal function and also indicate one way in which renal lesions affect the body as a whole and make of Bright's disease not

merely a form of kidney disease but a disease of the entire body The amount of plasma protein or of its several components in 100 c c is an index but not a full measure of the more important total plasma protein of the body The latter can be determined by measuring both the amount in 100 c c of plasma and the plasma volume Marked quick shifts in the plasma volume can be estimated by blood counts by hemoglobin determinations or by hematocrit readings of blood and plasma volume

As already pointed out various methods are available for studying the composition of protein Of these the method of fractionating[a] by a process of salting out at various levels of concentration of the salt being used and the method of electrophoretic analysis which fractionates according to the speed of migration in an electric field of various proteins have been of very great service in the analysis of plasma proteins

Using the method of fractionation of proteins by salting out with increasing concentrations of Na_2SO_4 plasma protein can be separated into fibrinogen euglobulin pseudoglobulin I pseudoglobulin II and albumin their order of magnitude in normal plasma being albumin 100 pseudoglobulin I 23 pseudoglobulin II 17 euglobulin 17 and fibrinogen 7 according to Berglund and his associates[?] They give the composition of plasma protein in 19 normal individuals in grams per 100 c c in the following table

Fibrinogen	0 294 ± 0 010
Euglobulin	0 681 ± 0 062
Pseudoglobulin I	0 939 ± 0 049
Pseudoglobulin II	0 681 ± 0 041
Total globulin (including fibrinogen)	590 ± 0 050
Albumin	4 070 ± 0 070
Total protein	6 660 ± 0 090

In Bright s disease the composition of plasma protein may be very different as indicated in the following table based on a study of the plasma protein in practically the same number of patients as formed the basis of the preceding table of values for normals[43]

Fibrinogen	0 747 ± 0 057
Euglobulin	0 874 ± 0 075
Pseudoglobulin I	1 130 ± 0 030
Pseudoglobulin II	0 774 ± 0 021
Total globulin (including fibrinogen)	3 470 ± 0 110
Albumin	2 960 ± 0 080
Total protein	6 430 ± 0 120

Using electrophoresis fractionation with a different terminology for the protein fractions such figures as the following are obtained in grams of protein per 100 c c [65 66 69 306 307]

	Total protein	Albumin	Globulins alpha	beta₁	beta	gamma	Fibrinogen
Average of normals	6.5	4.06	0.46	0.31	0.55	0.75	0.37
Nephrotic	4.0	1.10	0.61	0.62	0.74	0.19	0.[illegible]4
	4.9	0.91	1.36	0.31	1.50	0. 5	0.59
	3.7	0.37	1.47	0.16	0.9	0.28	0.50
Terminal nephritic	6.0	3.11	0.33	0.40	0.92	0.85	0.39
	5.3	3.17	0.50	0.51	0.55	0.45	0.3
	6.6	4. 8	0.36	0.31	0.71	0.60	0.34

When both chemical and electrophoretic methods are used figures obtained for total protein albumin and globulin are comparable although not identical[69]

By electrophoresis at pH 4.0 serum albumin is separated into two components alpha and beta occurring in the same ratio in plasma and urine[66 306 307] In normal human plasma protein there is 67 per cent of alpha and 33 per cent of beta a ratio which is reversed in the nephrotic syndrome but not in terminal nephritic plasma[65 66 69] These results are shown also in the following figure (Fig 5)

In Bright's disease it is the albumin fraction of plasma protein that undergoes reduction Sometimes this reduction is very great The reduction of the albumin fraction is retarded by a high intake of protein in the diet The amount of the globulin fraction usually is increased when the plasma albumin is decreased The forms of Bright's disease in which urinary protein is largest cause the greatest change in the plasma protein fractions With marked renal insufficiency total plasma protein and variations in plasma protein fractions are less marked than when renal function is well preserved as in the nephrosis syndrome In acute Bright's disease the protein usually is little if any, different from values found in normal persons but in very severe acute nephritis a striking reduction in plasma albumin level with a corresponding rise in globulin may be found [0]

The ratio of albumin to globulin in the blood plasma is changed by excess in excretion of albumin as compared to globulin in the urine of patients with Bright's disease and particularly in those showing the nephrosis syndrome, in which as a rule the normal relation in which albumin exceeds globulin is reversed along with a usual but not constant decrease in the total plasma protein Variation in the metabolism of ingested protein also is a factor in variations in the plasma proteins

Using the electrophoresis technique more and more studies have been made of the composition of plasma protein showing not only the amount or proportion of albumin and globulin in the plasma of normal individuals and of patients with various forms of Bright's disease of varying severity but also the proportion

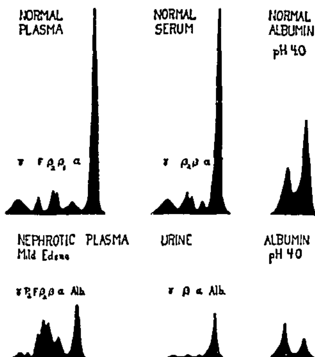


Fig 5 —Electrophoretic diagrams of normal plasma normal serum and normal albumin and of plasma urine and albumin of patient with nephrosis syndrome γ = gamma globulin F = fibrinogen β_1 β_2 = beta globulins (from Luetscher[60])

of the several components of the globulin fraction (Fig 6) A recent study[47] has shown in the plasma protein of a patient with very marked edema albumins 7 per cent and globulins 93 per cent the latter subdivided as follows alpha₁ globulins 4 per cent alpha₂ globulins 42 per cent beta globulins 28 per cent fibrinogen 16 per cent and gamma globulin 3 per cent in contrast to albumins 26 per cent and globulins 74 per cent the latter subdivided into alpha₁ globulins 22 per cent alpha₂ globulins 30 per cent fibrinogen 9 per cent gamma globulins 5 per cent in a similar patient with much slighter evidences of the nephrosis syndrome In contrast to these normal pooled human plasma showed albumins 55 per cent and globulins 45 per cent the globulins subdivided into alpha globulins 5 per cent alpha₂ globulins 9 per cent beta globulins 13 per cent fibrinogen 7 per cent and gamma globulins 11 per cent (Fig 6) Patients with chronic Bright s disease of the non edematous type or non nephrotic syndrome give plasma protein values in line with those from normal individuals and as the nephrotic syndrome decreases in patients with the edematous type of Bright s disease plasma protein values shift towards but not to such normal values Such a shift is shown in Fig 7

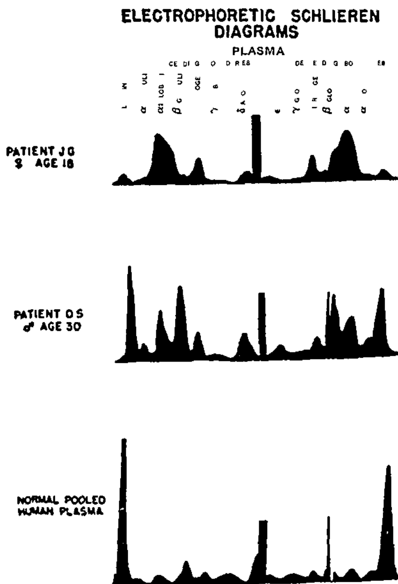


Fig 6 — Electrophoretic patterns of plasma from two patients J G and D S with edematous type of Bright's disease (nephrotic syndrome) in contrast to that of pooled normal human serum (from Thorn and Associates[372])

PATIENT J G

PLASMA

FEBRUARY 1944



AUGUST 1944



NOVEMBER 1944



Fig — A succession of electrophoretic patterns of plasma from patient J G with edematous type of Bright's disease (nephrotic syndrome) showing progressive changes probably of spontaneous rather than therapeutic origin occurring between February and November (from Thorn and Associates[373])

The decrease of the albumin component in the plasma protein of patients with the edematous type of Bright's disease so important in relation to osmotic tension and the development of edema also is of importance as an index, but not necessarily an exact measure of the depletion of tissue protein stores Obviously until the tissue protein store returns to normal it can not be claimed that the injurious effect on the patient of the renal lesion has been counterbalanced and that the patient again is in good health

Lipoids

Under the term lipoids, there are included as constituents of the blood true fats embracing neutral fat and fatty acids and additional substances resembling fat in general properties and particularly in solubilities, including lipids, phospholipids or phospatides and sterols the most important of which is cholesterol Under fasting conditions the lipoids in blood plasma amount to 400 to 600 mgm per 100 c c of plasma When these increase we use the term lipoidemia or hyperlipoidemia and the terms, phospholipemia and hypercholesteremia, when the increase is mainly in lipids or cholesterol

Normal values in blood plasma have been stated as follows neutral fat, 0 to 370 mgm per 100 c c with average 70 mgm, fatty acids 350 to 450 mgm with average 353 mgm, phospholipids, 60 to 350 mgm with average, 196 mgm, cholesterol 150 to 250 mgm with free cholesterol, 40 to 50 mgm and cholesterol esters 190 to 200 mgm

In chronic Bright's disease with edema, the nephrosis syndrome, lipoids usually are increased in the blood even enough to cause a milky appearance of the serum with values of 500 to 1 000 mgm per 100 c c of plasma At times very large amounts have been reported such as 2 300 mgm of cholesterol (Baehr[84]) and in another patient lipoids 4 700 mgm with 2 500 mgm of fatty acids 1 000 mgm of cholesterol and 1 000 mgm of phosphatides (Knauer[85]) The various fatty components usually rise and fall together but not to parallel degrees When renal insufficiency develops in the patient with the nephrotic syndrome blood lipoids and urinary protein tend to decrease

Diminution in lipoidemia also occurs when emaciation becomes marked, even if it is concealed by body edema In chronic Bright's disease without edema and with nitrogenous retention blood lipoids of all sorts decrease and hypolipoidemia and hypocholesterolemia may be found when the uremic stage is approached or reached in part caused by the anorexia and frequent vomiting which reduce greatly food intake and cause weight loss with reduction in adipose tissue in these patients Consequently in uremia hypolipoidemia and hypocholesteremia may appear In acute Bright's disease little change from normal lipoid values takes place

Mineral Metabolites

The amounts of the various mineral metabolites in the blood of patients with Bright's disease may show departures from the normal some more than others These changes take place more often to give values above normal sometimes however values decrease, usually they remain within the rather narrow limits considered to be normal These changes depend in part on disturbance in renal function in part on changes in ingestion and absorption and in part on variations in excretion by other routes than the urinary one The mineral metabolites of clinical significance in Bright's disease are the chlorides carbonates phosphates and sulfates of sodium potassium and calcium Their metabolism is important in the preservation of acid base balance particularly in the prevention of acidosis which tends to occur in severe Bright's disease and to cause serious symptom and in aiding in the maintenance of water balance and normal osmotic pressure in blood and tissue fluids

The following normal values of mineral constituents of blood serum are given chloride 352-383 mgm per 100 c c serum or 99-110 milliequiv per liter sulfates inorganic 0 9-1 5 mgm per 100 c c serum sulfates total 3-4 5 mgm per 100 c c serum phosphates inorganic 2-5 mgm per 100 c c serum sodium 315-340 mgm per 100 c c serum or 139-152 milliequiv per liter potassium 16-22 mgm per 100 c c serum or 4 1-5 6 milliequiv per liter calcium 9-11 mgm per 100 c c serum or 4 5-5 5 milliequiv per liter sodium chloride 350-390 mgm per 100 c c serum or 99-110 milliequiv per liter phosphorus inorganic 3-4 mgm per 100 c c serum phosphorus, total 35-45 mgm per 100 c c serum

Sodium and Chloride — In Bright's disease changes in the mineral metabolites sodium and chloride play the largest part in the mechanism of the disturbances that this disease causes Usually they decrease or increase proportionately but this is not always the case as for example in the excessive vomiting of the uremic patient in which chloride loss is in excess of sodium loss on account of the loss from the body of hydrochloric acid

Hypochloremia occurs in chronic Bright's disease both from excessive vomiting and from a failure of tubular reabsorption sometimes from fixation in the tissues Rarely a very interesting clinical syndrome closely simulating that of adrenocortical insufficiency develops as a result of a chronic renal lesion which causes an excessive loss of sodium chloride and water from the body with nitrogen retention[403] In these patients hypochloremia is very marked and a very large daily intake of sodium chloride and sodium bicarbonate is needed to control this condition The term salt losing nephritis has been suggested for this syndrome[403]

Slight hyperchloremia may be found in edematous type of subacute or chronic Bright's disease usually associated with hypoproteinemia and sometimes in

severe acute Bright s disease with oliguria In marked oliguria and in anuria very marked hyperchloremia may occur Braasch[84] reports a patient with plasma chloride reaching 1 500 mgm per 100 c c and Fishberg[85] one with plasma sodium chloride of 1 000 mgm per 100 c c Dehydration and edema influence sodium chloride content of the blood and give values for serum sodium and chloride which do not portray accurately their content in body fluids The erythrocytes contain normally about half as much chloride as the plasma, sometimes shifts of chloride from cells to plasma occur to change serum values, while the chloride content of the blood remains unchanged

Potassium normally 16 to 24 mgm per 100 c c of serum in contrast to 315 to 340 mgm for sodium changes relatively little in patients with Bright's disease With marked renal insufficiency sometimes it shows increase but usually not to a high degree Briggs[86] reports a case with 36 mgm per 100 c c Keith and associates [17] one with 41 mgm Potassium is abundant in red blood cells 420 mgm per 100 c c while there is little or no sodium in them Rarely a decrease in serum potassium occurs causing great muscle weakness[87]

Phosphate and Sulfate —An increase of serum *phosphate,* hyperphosphatemia occurs with renal insufficiency and acidosis An average normal of inorganic phosphate of 3 mgm per 100 c c, calculated as phosphorus may be increased in some patients to 28 mgm (Denis and Minot[88]) Similar changes take place in serum *sulfates,* and the two together play a causative rôle in nephritic acidosis In the nephrosis syndrome during periods of generalized edema there is phosphorus retention in one patient following a crisis there was a rapid disappearance of edema with an outpuring of phosphorus along with sodium and calcium in both urine and feces with slight reduction in serum phosphorus, 4 9 mgm per 100 c c to 4 6 mgm [373]

Calcium is increased beyond the normal of 11 mgm per 100 c c. of serum when there is marked renal retention as in uremia Besides such hypercalcemia, hypocalcemia appears more commonly in Bright s disease notably in those cases showing the nephrosis syndrome and in those developing uremia In patients with nephrotic type of edema there is an abnormally low serum calcium concentration with excretion of an abnormally great percentage of ingested calcium in the stools and a virtual absence of calcium in the urine[373]

Glucose

Blood sugar remains within normal limits in most non hypertensive patients with Bright's disease In the presence of hypertension without or with evidences of pathological changes in the kidney frequently there is found a moderate hyperglycemia but with it glycosuria is infrequent unless there is evidence of a definitely diabetic condition It would seem that in these patients the threshold for

glucose has been elevated This is not the result of general renal retention for often with marked nitrogen retention there is no hyperglycemia Two explanations have been offered for this situation (1) It is the result of a high blood diastase or amylase mobilizing an increased amount of glucose from liver and muscles (Myers and Killian[89]), however increase in blood diastase commonly accompanies more severe Bright s disease and is not present in essential hypertension in which hyperglycemia is frequent[169] (2) It results from damage to the islands of Langerhans in the pancreas from arterial lesions here part of the general presence of arterial lesions in these patients (O Hare[90]) these patients may be considered to be potential diabetics but relatively few of them progress into diabetes mellitus

In patients with marked albuminuria i e in patients showing the nephrosis syndrome, moderate often transitory glycosuria frequently occurs In them blood sugar levels are apt to be lower than normal Frequently an alimentary glycosuria can be demonstrated glucose threshold seems lowered[91] the condition behaves like a renal not a diabetic glycosuria This may be explained on the basis of deficient tubular reabsorption of glucose as an expression of the tubular lesion in this form of Bright s disease Very possibly also there is an increased filtration of glucose through the damaged glomerular membrane along with the escape of much albumin

In the discussion of edema dehydration acidosis alkalosis and uremia in the section headed Pathological Physiology further mention of changes in blood composition in Bright s disease including values of certain constituents not described in this section, will be found

Etiology

Acute Bright's Disease

In Bright's disease according to a conception of it favored by many at present three general types of lesions, as will be discussed and described in the section on Pathology are concerned each having a different etiology, one is primarily a glomerular lesion with consequent and subsequent lesions of the tubules and the renal blood vessels both those within and without the glomeruli another is primarily a lesion of the blood vessels, both within and without the glomeruli with consequent and subsequent lesions of the glomeruli and of the tubules, the third results from a chronic bacterial inflammation In all of them the clinical disturbances as will be seen later, are derived in the main from disturbances of glomerular function[2] with subsequent effects from changed tubular function[305] In our clinical classification the primarily glomerular lesions occur in acute Bright's disease subacute Bright's disease and chronic edematous Bright's disease while the primarily vascular lesions are found in primary chronic Bright's disease and in chronic Bright's disease subsequent to hypertension in chronic Bright's disease secondary to pyelonephritis, a bacterial inflammation the lesion is complex involving interstitial tissue glomeruli and blood vessels and is consequent upon an acute diffuse, bacterial inflammation

Infections of various sorts cause most of the cases of acute Bright's disease Longcope and his associates[9] could demonstrate an infectious focus in 85 per cent of their patients Ellis[318] in a similar group of his patients found causative infection in 84 per cent Infections of the upper respiratory tract in particular start the acute renal process which we call acute Bright's disease Tonsillitis and pharyngitis are the most frequent causes and so the streptococcus group must play an important role in the etiology of Bright's disease Hill[93] in a study of acute Bright's disease in children gives tonsillitis as the etiology in 22 of 81 cases and adds that among those tabulated as unknown 26 cases tonsillitis was an important factor as nearly all of the children in this group had large unhealthy looking tonsils Fishberg[94] in 455 cases tabulated from the literature gives angina (sore throat) as cause in 157 In adults at the Peter Bent Brigham Hospital the cause was attributed in the history to tonsillitis in 9, and to colds which probably included many that had tonsillar infection in 16 out of 66 cases of acute Bright's disease Infections of the paranasal sinuses and of the tooth sockets possibly are portals of entry Just how frequent this last type is we do not know It is assigned as the cause in but one of the Brigham patients Longcope[9] gives sinusitis as cause in 13 of 48 cases In this type the primary infection probably is overlooked frequently because the patient has become adjusted to its presence and has no acute reaction from an infected sinus or peridental abscess In such cases,

too a further difficulty arises inasmuch as with an existing infection at the tooth root one is not justified in saying that it has been the cause of the acute Bright s disease when these infections especially those about the teeth are so very frequent without being followed by such infectious processes as are represented by acute Bright s disease

In association with vegetative endocarditis there are cases of acute Bright s disease which although numerically not so very important are of much importance from the point of view of throwing light on the etiology and mechanism of at least one type of renal lesion These are cases in which bacteria mainly *Streptococcus viridans* in vegetations on the cardiac valves set up changes in the glomeruli They have been described by Baehr[86 87] and by Libman[88] and by them attributed to emboli of bacteria The present author[89] has described in kidneys from patients dead of *Streptococcus viridans* vegetative endocarditis the presence of a large variety of glomerular lesion and points out that all of these including those described by Baehr and Libman occur in kidneys of acute Bright s disease not associated with endocarditis as well as in experimental uranium nephritis He *does not regard them as caused by emboli of bacteria obstructing capillaries in* the glomeruli as did Baehr and Libman

Occasionally subcutaneous and other infections cause acute Bright s disease Following diphtheria pneumonia and erysipelas acute Bright s disease is relatively infrequent although typical cases are seen sometimes Any sort of an acute infection at times may start an acute Bright s disease After meningitis and typhoid acute Bright s disease is rare Curiously enough such a typical respiratory tract infection as influenza very seldom leads to acute Bright s disease at least that was my experience in the 1918–19 epidemic although many cases were described following earlier epidemics

The infectious diseases particularly the acute exanthemata like the acute infections just discussed very often have acute Bright s disease as a complication or sequel Scarlet fever in particular is a frequent offender in this respect and the Bright s disease of scarlet fever constitutes one of its s rious dangers Fishberg[84] in his collected cases gives 56 out of 455 as so caused Hill[93] however thinks that in children more cases are secondary to tonsillitis than to scarlet fever Measles very much less frequently causes an acute Bright s disease while the other exanthemata are quite infrequent causes Certainly in scarlet fever and probably *in measles the streptococcus plays an important causative role in the* complications in scarlet fever it probably is the primal cause In certain epidemics of infectious diseases Bright s disease is more frequent than in others this is not merely from an increased severity of the disease All have long noted that severe acute Bright s disease may follow a mild attack of scarlet fever or that in one group of cases of scarlet fever Bright s disease is particularly common In such cases there may be a difference in the strain of organism or there may be

a difference in local resistance of the kidney Whatever the explanation, the fact remains that this great variation in incidence of acute Bright's disease occurs after all infectious processes It is a subject on which further light is needed, particularly to apply in the prophylactic management of these diseases to prevent Bright's disease

From the types of infections, mentioned above, it is evident that the streptococcus group plays a large role In 116 cases of acute glomerulonephritis Lyttle and his associates[115] found evidence of prodromal hemolytic streptococcus infection in 71 5 per cent and immunological data indicating streptococcic etiology in 94 per cent Tonsillitis and sore throat are almost always due to hemolytic streptococci In the apical infections of teeth *Streptococcus viridans* usually is the predominating organism although the hemolytic type may be present Acute vegetative endocarditis as a rule is due to the *Streptococcus viridans* In the infectious diseases, particularly in scarlet fever streptococci of the hemolytic group are always present and probably are the cause of most of the complications including Bright's disease Hemolytic streptococci are responsible for some of the other infections that precede acute Bright's disease It is probable that hemolytic streptococci cause most of the cases of acute Bright's disease, that the viridans type may be a cause is shown by the renal lesions often found with acute and subacute vegetative endocarditis Other pyogenic bacteria may be an occasional cause

Much discussion has arisen in regard to the relation of syphilis to renal lesions One group of observers considers that *renal disturbances following syphilis result from the action of the drugs, mercury and arsenic used to treat the* syphilis As syphilis is treated today this seems hardly a tenable explanation although I am quite sure an existing Bright's disease very definitely may be made worse by the mercury and arsenic used in the therapeusis of syphilis a fact which calls for caution in using these drugs in the presence of evidences of Bright's disease However it is sure that this caution should not go so far as to prevent the proper treatment of a syphilitic affection Another group of observers believes that acute renal lesions frequently follow syphilis particularly in the later stages of an extensive secondary type of lesion Unquestionably, evidences of renal irritation are frequent but I have never seen a case of syphilitic Bright's disease, although the literature contains accounts of cases which in their relation to other syphilitic lesions and to antisyphilitic treatment seem to be reasonably clearly a matter of cause and effect The nephrosis type of Bright's disease may be caused at times by syphilis according to some reports

To intestinal intoxication acute Bright's disease sometimes is attributed That bacteria may find this portal of entry open and therefrom reach the kidney and cause Bright's disease seems probable but direct evidence of this is relatively slight Just what may result from the absorption of toxic substances formed in

the lumen of the intestine in the process of normal or abnormal digestion is largely unknown, speculation here is far more common than presentation of careful observations That such substances could cause lesions in the kidney seems entirely plausible but there is very little real evidence that they do so Intestinal intoxication or autointoxication of intestinal origin or absorption accompanying intestinal stasis are all catchwords to the theorist Food intoxication apart from botulism has lost caste rapidly in the light of modern studies Ptomaine poisoning is probably a myth It seem that apart from the entry of bacteria the intestinal tract is not a proved source of acute Bright s disease This question will be referred to again when chronic Bright s disease is discussed

Pregnancy certainly is a pretty frequent cause of acute renal disturbance It is not certain whether this is of the nature of an acute Bright's disease or not Probably the lesion is quite different from that in most of the cases of acute Bright s disease of other origin Clinically when the condition is advanced there is decreased urine with abundant albumin and casts edema usually is present and often is extensive blood pressure generally is high and the patient is toxic the process going on to convulsions Marked hematuria is not common although the sediment usually shows a few red blood cells This is not the picture of the usual acute Bright s disease Following emptying of the uterus the process as a rule clears quickly and the kidneys later show little evidence of damage This is a toxemia of pregnancy and is more than an acute Bright s disease The real cause of the condition seems to me to be unknown It is in some way associated with pregnancy but just how is not known That the pregnancy in itself causes it is a statement not justified If it is considered as an acute Bright s disease then pregnancy indirectly is a frequent cause of acute Bright s disease if this particular type of renal disturbance is considered as a thing apart from the ordinary *types of Bright s disease then pregnancy is a very infrequent cause of acute* Bright s disease It seems to me that the kidney lesion of pregnancy is better considered as a manifestation of eclampsia and described in connection with it rather than described as a form or type of acute Bright s disease So far as my experience goes the two conditions are really quite different and the subject is clarified if the two are kept separate, even if not regarded as entirely different processes

Various toxic substances such as corrosive sublimate arsenic lead etc are quite capable of producing an acute Bright s disease Many of these substances when injected into animals produce renal lesions quite identical with those found in acute Bright s disease in man Practically in man such substances rarely are causative factors in acute Bright s disease except when they intentionally or by accident are taken in highly toxic doses as in corrosive sublimate poisoning Alcohol and tobacco although incriminated in this way by some reveal little evidence that can be adduced to show that they cause Bright s disease Following

the abuse of alcohol acute Bright's disease not infrequently develops, but it seems probable that infection indirectly related to the alcohol, is the direct cause of the Bright's disease

The action of these simple toxic substances, such as corrosive sublimate and uranium nitrate in producing an acute experimental nephritis is of very great interest as having thrown much light on the subject of acute Bright s disease in man They produce in animals lesions in every way identical with what we find in man both degenerative and proliferative lesions of the glomeruli and of the tubular epithelium Introduced intravenously or subcutaneously they may cause little change except in the kidney, showing that with them there is a selective action either by reason of cell affinity or on account of the concentration that takes place during excretion through the kidney This selective action is not alone for the kidney in contrast to other organs but for special parts of the kidney such as the marked action of uranium nitrate on the proximal convoluted tubule, while largely sparing other portions of the tubule Again, their action often is focal and not generally diffuse The lesion produced in a given structure within the same kidney, moreover, is a varied one, for example, a variety of glomerular lesions both proliferative and degenerative, may be found in the kidney after injection of uranium nitrate[100 101] while degeneration of the epithelium of the tubules is practically constant These results in experimental lesions produced by very simple chemical compounds make it clear that circulating toxins can be expected to produce focal or general lesions, and that these lesions may vary much in type when due to the same toxic substance

Exposure to cold long has been regarded as a potent cause of acute Bright's disease Quite certain it is that attacks of acute Bright s disease do follow chilling of the body but here an acute infection rather than congestion or anemia caused by the chilling may be the responsible factor Perhaps the chilling lowers resistance and allows bacteria to enter and develop with various lesions, including those of Bright s disease in their train Here the relation would be much that of the chilling to an attack of pneumonia the pneumococcus is the real or prime cause the chilling is a contributing factor I am inclined to think that the chilling in itself and alone is not a cause of acute Bright's disease, if it is a cause, it is an infrequent one

Viruses do not seem to be causative of Bright s disease, and the same may be said of vitamin deficiency

For the relation of causative organism to renal lesion of acute Bright s disease see subsequent section Pathogenesis of Renal Lesions of Bright s Disease

Chronic Bright's Disease

Infections and infectious diseases cause the greater proportion of the cases of acute Bright's disease. In finding out the etiology of chronic Bright's disease the difficulties are far greater. For many patients there is no active or acute period of onset; some cases of chronic Bright's disease, however, develop as a recognized progression from an acute Bright's disease; the etiology of these is as already discussed in the preceding section. In some patients there is a recognized acute Bright's disease, then a quiescent period of apparent normality, period of latency, and then the symptoms and signs of chronic Bright's disease appear; but a very striking feature of very many of the histories of patients with chronic Bright's disease is the absence of anything suggestive of an antecedent attack of acute Bright's disease. Certainly numerous patients with acute Bright's disease fail to develop later evidences of chronic Bright's disease.

In assigning a cause for acute Bright's disease we were helped by the frequent close relation of some infection or infectious disease to the onset of the acute Bright's disease. For chronic Bright's disease we do not get such help as often because in so many patients there is no close relationship between onset of symptoms and infection or infectious disease. In fact, usually it is almost impossible to determine when the chronic Bright's disease really did begin. Again, almost all individuals, by the time they reach adult age, have had one or more of the infections or infectious diseases supposed to cause acute Bright's disease; consequently a past history of such in a patient with chronic Bright's disease who gives no history of an attack of acute Bright's disease is of no help; statistically it would not be very different from the incidence of the same infections and infectious conditions in people free of Bright's disease. If we assume that these infections and infectious diseases do cause chronic Bright's disease, then it is even more difficult to explain why, in so many people, they occur without producing Bright's disease. This is not saying that infection and infectious diseases are not important causes of chronic Bright's disease; they probably are; but the reason for the statement lies in probable analogy to acute Bright's disease and in observations on a few cases of chronic Bright's disease with definite acute or abrupt onset following infection or infectious diseases. This is far from satisfactory proof and can give no basis for forming any idea of relatively what proportion of patients with chronic Bright's disease have the condition as a direct result of infection or infectious disease.

The cases of subacute or chronic Bright's disease with edema much more frequently than the other group have an easily assigned definite onset, but close relationship to infection or infectious disease is not frequent even in these patients. Some pathologists, however, think that kidneys with extensive glomerular lesions often give evidence of a bacterial etiology of the process.

Chronic Bright's disease without edema, i e chronic primary Bright's disease and chronic Bright's disease subsequent to hypertension of the clinical classification has no definite etiological relationship to infection or infectious disease in so far as evidence, such as we can get goes They may have such an origin but we cannot prove it Statistics of our Peter Bent Brigham Hospital cases of vascular hypertension prepared by O'Hare and Walker[10] show that there is no increased incidence of infections and infectious diseases in the past histories of these patients as contrasted to non hypertensive hospital patients of the same general age, social status and occupation On the other hand recurring infections may play a part in determining the progression of the lesion especially when they produce the clinical picture of an acute exacerbation

Chronic infections such as tuberculosis leprosy and syphilis appear to be of very little importance as causes of chronic Bright's disease Chronic poisoning such as from lead unquestionably can cause chronic Bright's disease as is shown by animal experimentation and by observation of human cases but it seems inconceivable that such causes can contribute many of the very large number of cases of chronic Bright's disease that we see

The relationship between food and chronic Bright's disease is an interesting one about which there has been more speculation than observation Too much food the wrong food defective digestion have all been assigned as causes of chronic Bright's disease Some experiments of Newburgh[103] in the production in animals of renal lesions when fed diets very high in protein are interesting and suggestive in this connection Newburgh finds that a diet high in either animal or vegetable protein causes in rabbits lesions resembling those of chronic Bright's disease with albumin and casts in the urine as well as vascular lesions like arteriosclerosis Some have thought that the changes may have resulted from a defective ill balanced, diet rather than from the high protein content or from feeding a very unnatural diet With this in mind in McCollum's laboratory in Baltimore McCollum Simonds and Polvogt[104] conducted experiments on rats with a balanced though high protein diet a diet, which was adequate for normal propagation and growth With it they report the occurrence of renal lesions However careful reading of their paper shows that the lesions found are slight and apparently acute in nature It seems strange that if they are in any sense a real Bright's disease that growth is normal Mendel and his associates (personal communication) at Yale conducted similar feeding experiments on rats and found that the rats in every way were normal except for much enlargement of the kidneys This they consider a work hypertrophy and not a pathological lesion If it turns out that Newburgh's conclusions are correct they are in accord with the clinical observation that high protein feeding often is harmful to the patient with a well marked chronic Bright's disease

The possibility of the wrong food rather than too much of it as a cause of

chronic Bright s disease is deserving of some consideration We recognize now the possibility of body disturbance from repeated or chronic anaphylaxis Longcope[103] has published some suggestive experiments indicating that anaphylaxis may lead to chronic renal lesions the reservation however needs to be made here and it is applicable to all experimental chronic renal lesions that we do not feel sure that the procedure which was carried out produced the observed lesion either directly or indirectly the lesion may have been spontaneous and totally unrelated to the experiment This entire question of the relation of food in an anaphylactic or other sense to chronic Bright s disease needs further investigation with trial diets and tests of the protein sensitivity of the patients Skin tests made in the Brigham clinic showed no special skin sensitivity to food proteins in a group of patients with chronic Bright s disease

The possible relationship between the absorption of food products partially metabolized when there is disturbed digestion the absorption of toxic material resulting from intestinal fermentation and putrefaction the relation of chronic constipation and the possibility of the formation of toxic material in the metabolism of food in some part of its course between ingestion and final utilization are all important considerations when the etiology of chronic Bright s disease is being discussed Here our present knowledge justifies little more than speculation Over-eating eating improper food imperfect digestion etc may play a considerable part in the etiology of chronic Bright s disease beyond that we cannot go at present There again is a field in which careful and prolonged observation and experimentation are needed

Vitamin deficiency seems to play no causative role in the development of chronic Bright s disease

Alcohol often is assigned an important role in causing chronic Bright s disease For this there seems to be no real proof and very little if any acceptable evidence Gout often is associated with chronic Bright s disease and may be a causative factor These cases however make up a very small proportion of the cases of chronic Bright s disease at most and of the real primal cause of gout we know almost nothing

The entire question of the causes that lead to the production of chronic renal disease is intimately related to that of the causes of chronic vascular disturbances particularly those associated with hypertension Changes in the vascular supply often may be causative in lesions of the kidney since so many of our patients give evidence of an antecedent hypertension also failure in the excretory function of the kidney may lead to disturbances operative in the production of vascular lesions We feel quite sure that an intimate relationship exists here but the ultimate causes are extremely poorly understood

The etiology of those forms of Bright s disease primarily vascular in nature is far from solved as is true of vascular lesions in general except those caused

by syphilis, the latter, however, do not occur except rarely in the kidney of Bright s disease and do not seem productive of renal lesions analogous to those found in Bright s disease Numerous theories as to the etiology of the vascular nephritides have been offered running the gamut of infections toxic lesions hormonal influences, endocrinal disturbances, functional and organic nervous system disturbances degenerative processes obesity heredity and injury of the vessel wall by high blood pressure singly or in combination Heredity seems to be an important etiological factor in from 20 to 70 per cent or more of the patients according to different reports O'Hare, Walker and Vickers[106] elicited a family history indicative of hypertension in 68 per cent of 300 patients with hypertension in contrast to its occurrence in 37 6 per cent of 437 controls Weitz[107] found no history of it in only 6 of 82 patients with hypertension Ayman[108] found that in families in which both parents had normal blood pressure, only 3 1 per cent of the children had high blood pressure in contrast to 28 3 per cent, when one parent had hypertension and 45 5 per cent, when both parents were hypertensives

Hypertension directly or indirectly is the cause of the renal disturbance in those cases which may be classified as chronic Bright's disease subsequent to hypertension and may play some causal part in the further progression of vascular lesions when the high blood pressure seems to be caused by the renal lesion of Bright s disease It is possible that the vascular lesion is caused by some toxin or is the result of what begins as a degenerative lesion, but the evidence for such etiology is slight at best

That essential hypertension is hormonal in cause is a view supported but by no means proved by hypertension produced experimentally and with this go vascular lesions in the kidney, that a hormonal factor may play a part in causing the vascular lesions of some forms of chronic Bright s disease however, lacks convincing proof High blood pressure and vascular lesions accompany some endocrine disturbances but there is no proof that the endocrinal disturbances play a causal part in the renal vascular lesions of Bright's disease

Infections do cause vascular lesions, but in the vascular type of Bright s disease there seems to be no demonstrable relationship to previous infections, including focal infections at one time considered to be of much significance in the etiology of chronic Bright's disease The treponemes of syphilis cause lesions of the blood vessels with very great frequency and yet they appear to have only the rarest etiological relationship to any form of Bright s disease The virus organisms also seem to have no etiological relationship to it

From all of this one can conclude that except for the influence of heredity the etiology of the vascular type of Bright s disease is unknown and just how heredity the most commonly occurring antecedent, causes the vascular lesions in these kidneys is not understood

The form of Bright s disease secondary to pyelonephritis is the result of the chronic changes which follow bacterial infection of the kidney whether the causative bacteria originally reach the kidney as an ascending infection along the ureters or by an hematogenous route to cause acute infection it is in large measure but not entirely the result of the healing process of an inflammatory lesion The etiology of this type of chronic Bright s disease is of all of them the one most thoroughly understood

PATHOGENESIS OF RENAL LESIONS OF BRIGHT'S DISEASE

In the majority of patients, who develop acute Bright's disease, there has been so definite a relation to an infection as to make almost certain an etiological relationship to infection and most often, a streptococcic one The dominant lesion in the kidney of these cases is glomerular with accompanying but less significant changes in the cells lining the tubules [1,3] the former are largely proliferative in character the latter degenerative Just what relation exists between the causative organism of the infection and the kidney lesion is not entirely certain Three possibilities need to be considered (1) causative bacteria may circulate to the kidney and by their presence in the kidney cause the lesions, (2) the causative bacteria may produce toxins in the pathological process they are causing outside of the kidney as in the throat in tonsillitis and these toxic substances reaching the kidney in the process of excretion from the body may damage the structures of the kidney and cause consequent pathological lesions, (3) by the presence of circulating products of infection sensitization of the kidney has developed and then the changes that appear subsequently are an allergic response of sensitized tissue to a circulating allergen formed in the primary locus of infection

Of these possible relationships of causative organisms to kidney lesions in Bright's disease that of their direct presence in the kidney has relatively little support in either the microscopical examination of kidney sections or culture of bacteria from that organ, from the circulating blood or from the urine Longcope and his associates[9] and Friedemann and Deicher[1] only rarely could grow bacteria from blood or urine in patients with acute glomerular lesions Bell and Hartzell[110] demonstrated them in the kidney of only 1 of 11 cases Even in subacute bacterial endocarditis, as a rule I found no bacteria in sections of the kidneys Ophuls[111] however in his careful studies did believe that bacteria found their way to the kidney and acted locally, stating that "the cause of true nephritis is continued bacterial septicemia and the lesions in the kidneys are probably due to rapid bacteriolysis and incidental liberation of large doses of toxic material in and about the affected glomeruli Opposed to this view of lesion from local lodgement of bacteria is the great infrequency of renal lesions like those found in acute Bright's disease in patients dead of such conditions as pneumonia and typhoid with positive blood cultures or streptococcus, gonococcus and meningococcus septicemia With very prolonged bacteremia glomerular lesions seem to occur more frequently than in acute severe septicemia, but this fits better with the second and third possible relationship than with the first one which is under discussion here

The second possible relationship of infection in producing acute Bright's disease predicates the formation of a toxic product in the growth of the bacteria at

the site of the primary inflammatory process and its circulation to the kidney where it comes in contact with and damages structures of the glomeruli and tubules thus producing the lesions that appear Somewhat analogous to this is the view of Ophuls [11] and others that the bacteria themselves reach the kidney undergo bacteriolysis there and so free toxic products locally to injure renal structures and cause the lesions that there appear My own studies[12] of the kidney in *Streptococcus viridans* endocarditis gives some support to this latter view That the streptococcus with so prominent a role in the etiology of acute Bright s disease forms a powerful circulating toxin is well known its formation has been demonstrated by Dochez[13], the Dicks [13] and Trask and Blake [14] in their studies of scarlet fever and by others in investigations of other infections with the streptococcus and the additional organisms which appear to play a role in the etiology of Bright s disease Any toxin in the circulation would come in contact with the thin walled vessels of the glomeruli of the kidney and in these rate of flow is relatively slow, so that there would be opportunity for any predicated injury of the glomeruli to take place All of the changes which are seen in the glomeruli in the kidneys of acute Bright s disease are interpreted usually as the direct result of some injury or reaction to it or to proliferation stimulated by the presence of some substance not normally circulating through the kidney The tubules do not have such a direct relationship to assumed circulating toxins but since the capillaries about the tubules contain blood that has passed through the glomeruli they contain toxins not fixed in passage through the glomerular capillaries and these toxins could cause injury to the cells lining the tubules Also there is the possibility that toxins might be excreted through the glomeruli into the forming urine and so reach the surface of the cells lining the tubules These are definite possibilities if not demonstrated facts to use in explaining the pathogenesis of renal lesions According to this explanation the renal process is the result of injury by a toxic substance The diffuseness of the lesion in the kidney as well as the evidence of wide spread capillary damage in acute Bright s disease also speak in favor of this toxic nature of the process

The delay in the appearance of acute Bright s disease after the development of acute tonsillitis scarlet fever and other infectious processes its almost universal appearance as these processes are quieting down or even after convalescence from them is well under way *does not harmonize well with either of the two relationships* of the infectious process to the etiology and pathogenesis of the lesions of acute Bright s disease already discussed but is in harmony with the idea that the lesions in the kidney represent an allergic process first a sensitization of renal structure to a circulating toxin and then changes developing as an allergic response to a circulating allergen Various observations in man and experiments in animals are in harmony with this allergenic explanation and it is coming to be the one

generally accepted at present by students of the problems of Bright's disease. Among these observations are (1) the delayed development between onset of the primary infectious process and the appearance of the symptoms and signs of acute Bright's disease in contrast to the much more speedy appearance of evidences of an acute exacerbation in chronic Bright's disease following an infection such as that of the upper respiratory tract (2) the experimental production of renal lesions by injecting allergens into the general circulation or into the renal artery of sensitized animals, horse serum, egg white, heat killed hemolytic streptococci autolysates of pneumococci, living streptococci variously treated or injected over long periods of time tuberculin etc [11 1] (3) the production in animals of changes like those of acute Bright's disease by injecting anti kidney sera[1 3 1 7] and (4) clinical manifestations sometimes seen in serum sickness which point to a renal involvement[117 1 8], such manifestations as oliguria chloride, water and nitrogen retention albuminuria, cylindruria and edema, all of which disappear with the end of the serum sickness

All three of these explanations have in common some form of renal injury, most evident in the glomeruli less evident in the tubules causing degenerative and proliferative changes in their structures and allowing the escape into the urine of albumin red blood cells and casts All of the changes seen in the kidneys of acute Bright's disease described in the section on Pathology, can be understood in their development on the basis of local injury to renal structures and coincidental or subsequent proliferation or repair changes which involve both glomeruli and tubules but with a dominance of glomerular changes in their influence on renal function To this there seems to be very general agreement

As to the pathogenesis of the nephrosis syndrome there is less agreement In the opinion of the present author[1 9 180] the nephrosis syndrome is in mechanism like the other forms of acute Bright's disease it is pathologically a form of glomerulonephritis or glomerulitis which may heal, or which may show later the clinical findings associated with other forms of acute glomerular lesions and like them progress into subacute or chronic Bright's disease with the pathological appearances of subacute or chronic glomerulonephritis It has the same relation in its development in some patients to infection particularly streptococcic infection as do the non nephrotic types of acute Bright's disease just discussed The lesion primarily is of a nature to damage the glomeruli so that albumin escapes freely through the wall of the glomerular capillaries and is less than normally reabsorbed by the tubules of the kidney, which also have been damaged In most adults the damaged glomeruli also allow the escape of some red blood cells, while in children usually this does not occur or occurs to a less extent The glomerular leakage just noted seems satisfactory evidence that the lesion in this type of Bright's disease is a glomerular one disturbing the normal filtration function of

the glomerulus In the early stage in fatal cases there is very little change in the glomeruli that can be demonstrated under the microscope what is seen is a slight hyaline change in and slight thickening of the wall of the capillaries of the glomeruli best demonstrated by special stains[1, 13, 133] In some patients especially children, this process appears to heal allowing again normal glomerular filtration In an occasional patient this process continues with exacerbations and defervescences over a long period without healing and without further progression usually these are older children or young adults In a very rare patient thickening of the walls of the capillaries of the glomeruli continues and becomes sufficient to retard blood flow through the glomeruli and to cause symptoms as are encountered in patients with the lesions of a chronic glomerulonephritis[1, 6] In a large majority of the patients, almost always adults the glomeruli develop the same lesions as occur in the non nephrotic type of acute Bright's disease and progress often with acute exacerbations to subacute and chronic Bright's disease with corresponding chronic changes in the glomeruli In many of these progression is steady with or without acute exacerbations in others there is a period of months even of years of latency with freedom from symptoms and then a progression to chronic Bright's disease begins In these healing has been illusory

In the nephrosis syndrome many observers stress the lipoid deposits in the cells lining the tubules some of which are doubly refractive some not and regard this as the chief lesion disturbing renal function Others believe that this lipoid deposition takes place as the result of the marked lipoidemia this being a compensatory process in the train of the hypoproteinemia and not an evidence of tubular degeneration pointing out that in the normal cat tubular epithelium is laden with lipoids and yet seems to function normally Still others consider the lipoid deposits as analogous to other xanthomatoses a disturbance of lipid metabolism

The pathogenesis of subacute and chronic Bright's disease depends on the type of lesion in the kidney If this is mainly of the glomeruli two sets of changes take place both often present in the same kidney In one of these proliferation with subsequent degeneration of endothelial cells or thickening of the capillary walls by pericapillary fibrosis often followed by hyaline transformation and contraction results in impeding blood flow through the capillaries and this checks activity of function of the glomeruli Also changes in the capillary wall retards filtration and sets up retention in the body of various constituents of the blood stream normally being removed by excretion into the urine In the other of these changes proliferation of extracapillary epithelial cells occurs with subsequent degeneration and ingrowth between the cells of connective tissue fibrils shrinking and sclerosing the glomeruli impeding both glomerular blood flow and

glomerular filtration and decreasing or stopping the functional activity of the glomeruli

In another group of cases of subacute and chronic Bright's disease the lesion is mainly of the small arteries and arterioles with progressive thickening, hyaline transformation and fibrosis of their walls hindering free circulation through them When this change takes place, as it usually does, in the afferent and efferent arterioles of the glomeruli and extends into the capillary loops of the glomeruli and progresses glomerular function steadily is decreased, glomeruli become increasingly sclerosed and atrophied, finally cease to function and may disappear

As all glomerular lesions, which involve blood flow through them, influence circulation to the tubules, because most of their blood supply passes through the glomeruli before reaching them, these lesions in the glomeruli indirectly lead to degeneration and atrophy of cells lining the tubules and hinder, too their function as has been shown in studies using functional tests with inulin and diodrast during the progression of the disease

In both of these types of subacute and chronic Bright's disease atrophy of glomeruli and of tubules goes on, and as a compensatory process or as the result of interference with circulation interstitial tissue proliferates and later fibroses This becomes a factor in the progressive shrinkage in size of the kidneys that takes place in the majority of the patients with chronic Bright s disease, resulting finally in small kidneys of decreased functional activity

When there has been an acute or a subacute pyelonephritis, very similar changes as those just described take place to result eventually in damaged and atrophied glomeruli and tubules and increased interstitial tissue with progressing atrophy of the kidneys with the same disturbance in renal function as occur in these other forms of chronic Bright s disease

In all of these types of Bright s disease, in which glomerular lesions primarily non vascular or vascular occur a mechanism is set up, which tends to raise blood pressure so that in chronic Bright s disease of any sort hypertension usually develops and this largely may dominate the later stages of the clinical picture leading to a complicating cardiac hypertrophy and consequent cardiac insufficiency

Pathology

Kidney

On a structural basis Bright's disease or nephritis the latter term naturally being preferred by pathologists can be classified as follows

Acute Glomerulonephritis	Acute Vascular Nephritis
Acute Interstitial Nephritis	Subacute Glomerulonephritis
Acute Tubular Nephritis	Subacute Pyelonephritis

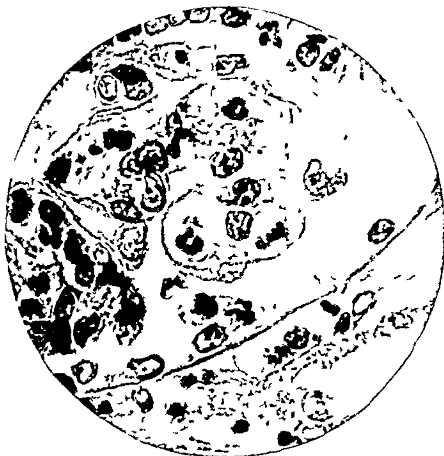


Fig 8 — Glomerulus showing proliferation of endo- and peri-capillary cells and hyaline thickening of capillary wall

glomerular filtration and decreasing or stopping the functional activity of the glomeruli

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FIG 10 — Glomerulus showing proliferation of endo- and peri-capillary cells

sclerosis atrophy and for some disappearance of glomeruli Glomerular lesions may be focal or diffuse in distribution in the kidney

Although focal distribution is seen usually most of the glomeruli show lesions in fatal cases Focal distribution probably indicates a mild degree of nephritis An attempt to form of this a clinical type of Bright s disease focal Bright s disease has been made justified by finding mild symptoms and signs and with clinical recovery sometimes a persistence of albumin and casts in the urine indicating that although the majority of the glomeruli now have become normal scattered ones i e a focal distribution have persisting lesions to cause albumin and casts in the urine Fishberg[85] uses the term acute focal glomerulonephritis

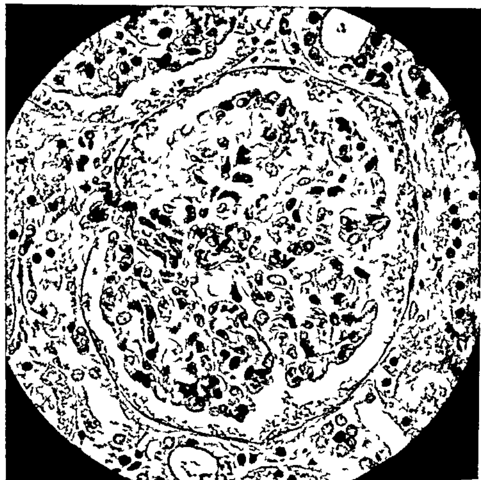


FIG 9 — Glomerulus showing proliferation of endo- and peri capillary cells

Chronic Glomerulonephritis	Various Acute Degenerative Lesions
Chronic Vascular Nephritis	Amyloidosis
Chronic Pyelonephritis	Myeloma Kidney
Intercapillary Glomerulosclerosis	Renal Cysts
(Kimmelstiel Wilson lesion)	Polycystic Kidney
Cortical Necrosis	Aplasia of the Kidney

Glomerular lesions may be subclassed as acute intracapillary proliferative acute capsular proliferative, acute hyaline capillary degenerative acute capillary thrombotic, subacute stages of these chronic stages of the preceding progressing to

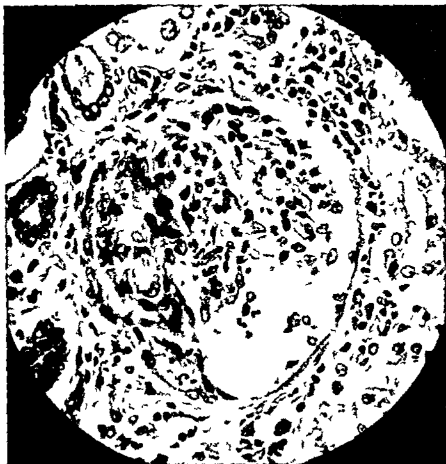


Fig 12 — Glomerulus showing epithelial crescent formed by proliferation of cells lining Bowman's capsule

involvement and the two can not be distinguished during life clinical use of the term focal glomerulonephritis or focal Bright's disease does not seem to the author worth while some clinicopathological studies[1] throw doubt on its existence as a diagnosable clinical condition which is in accord with the author's experience

It is of further interest that although according to Fishberg's views as just noted focal glomerulonephritis should occur very frequently it has received very little attention from those interested in the problems of Bright's disease the present author being able to find very few papers with a title containing the words

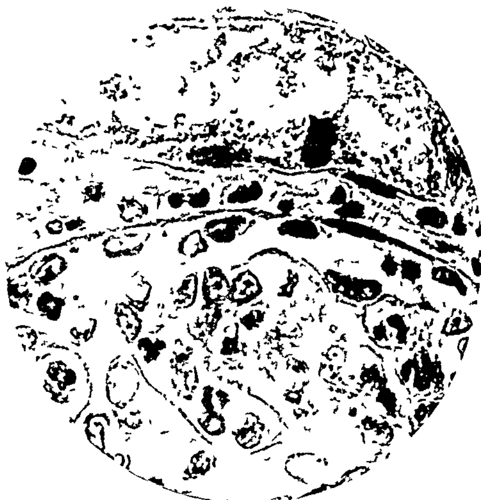


FIG 11 — Glomerulus showing hyaline thickening of wall of capillaries

when during the course of an infectious disease, hematuria, albuminuria and cylindruria occur in the absence of edema and hypertension He thinks that in these patients the bacteria act directly on the glomeruli and frequently can be obtained in cultures made from their urine The latter is in contrast to diffuse glomerulonephritis in which bacteria rarely can be found in the kidney sections or grown from the urine in diffuse glomerulonephritis he considers the lesion in the kidney to be of the nature of an allergic response Such focal glomerulo nephritis Fishberg finds to occur most often with streptococcal diseases and infec tions and much less frequently with pneumonia, typhoid and relapsing fever However, since the same clinical findings can result from mild diffuse glomerular

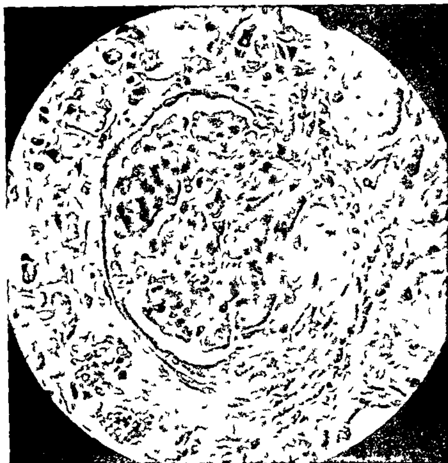


Fig 14 — Glomerulus showing epithelial crescent in process of hyaline fibrosis

process e g acute intracapillary proliferative glomerulonephritis etc The earliest changes found in the glomeruli are either multiplication of the cells of the glomerular tuft (Figs 9 and 10) or hyaline (Figs 8 and 11) transformation of the basement membrane of the loops of the tuft or of the capillary wall[121–134] often both lesions are seen in the same glomeruli Some believe that the hyaline capillary changes always antedate the cellular proliferation The endothelial cells of the capillaries of the tuft and the epithelial or mesothelial cells just outside the capillaries proliferate and usually the former increase in number much more than the latter The hyaline change may be the only abnormality seen in patients[131 132] who have the nephrotic syndrome it may require special staining methods for its

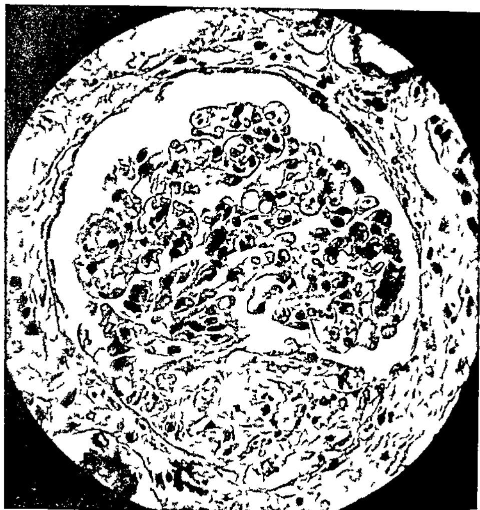


Fig 13 — Glomerulus showing epithelial crescent in which cells are undergoing hyaline degeneration

focal Bright s disease or focal nephritis, in the Quarterly Cumulative Index of the A M A from 1917 to date, and some of these refer to the renal lesions in subacute bacterial endocarditis Payne and Illington[13] have such a paper on focal nephritis but do not favor the use of the term Gross and Morningstar[150] describe focal glomerulitis in elderly patients but scarcely make out of it a definite entity I saw no papers except these discussing focal glomerulonephritis other than that in subacute bacterial endocarditis

As a rule in any kidney the glomeruli show a variety of lesions[133 134 168], although one type of lesion may so predominate as to justify giving its name to the

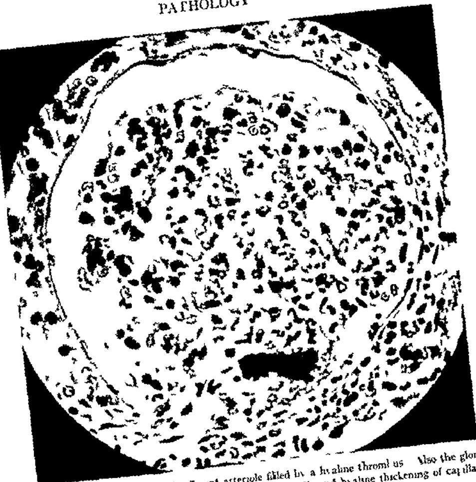


Fig 16 — Glomerulus with afferent arteriole filled by a hyaline thrombus Also the glomerulus shows proliferation of endo- and peri-capillary cells and hyaline thickening of capillary walls

demonstration[137] strictly speaking this lesion is an acute vascular nephritis as discussed later on in this section With extensive cell proliferation particularly of the endothelial cells we have acute intracapillary proliferative glomerulonephritis Another change usually not so early in appearance but sometimes the chief change is proliferation of the epithelial or mesothelial cells lining Bowman's capsule Very frequently this proliferation is at one part of the capsule to produce the so-called epithelial crescents this lesion is called acute capsular proliferative glomerulonephritis (Figs 12–15) Some speak of all of these lesions as forms of glomerulitis

In acute capillary thrombotic glomerulonephritis glomerular lesions composed



Fig 15 — Glomerulus showing epithelial crescent in process of hyaline degeneration and cellular capillary loops undergoing shrinkage to cause lobulation of the glomerulus periglomerular connective tissue has proliferated and is undergoing fibrosis

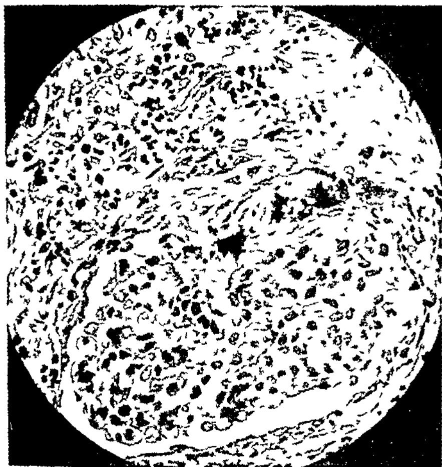


Fig 18 — Glomerulus with cellular proliferation and fusion between epithelial crescent and adjacent Bowman s capsule and glomerular tuft

of fibrin or of fibrin and proliferated frequently degenerated endothelial cell form to block the capillary (Fig 17) Formerly these were regarded as typical of subacute bacterial endocarditis and considered to be of embolic origin They occur however in kidneys from patients with various forms of infection in patients with acute Bright s disease of glomerular type and in rabbits poisoned with uranium nitrate as well as in the kidneys of patients dead of subacute bacterial endocarditis[99] To the author[99] they seem to be thrombotic rather than embolic in origin in some kidneys from patients with bacterial endocarditis emboli of bacteria may initiate these lesions and so they might be called thrombo-



Fig 17 — Glomerulus which is cellular and lobulated with fibrosis of interstitial connective tissue at one side



Fig 20 — Glomerulus showing more advanced stage of process shown in Fig 17 Now connective tissue has become increasingly acellular and hyaline

illary loops become adherent to Bowman s capsule with the cells about the former and those of the capsule proliferating and becoming continuous (Fig 18) Still later fibrils of connective tissue appear between the cells and increase in number while the cells undergo degeneration Also the few connective tissue fibrils normally in the stalk of the capillary tuft where the afferent and efferent blood vessels are increase in number thicken and extend out between the capillary loops to separate them more and more from each other all of these fibrils gradually thicken and shorten to exaggerate the lobulation of the glomerular tuft which now has decreased from its former swollen size and has an increased capsular

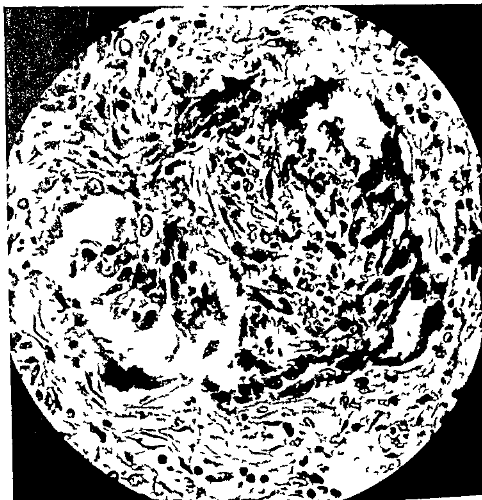


Fig 19 — Glomerulus showing diffuse proliferation of intraglomerular connective tissue and adhesions to Bowman's capsule at different points to form spaces lined with swollen epithelial cells

embolic or embolo thrombotic however most of them result from local degenerative injury of the inner surface of the capillary wall leading to the deposition of fibrin and to cell proliferation the cells later undergoing degeneration usually no bacteria can be found in them

As glomerular lesions persist, they undergo changes some of which are of the nature of a healing process and these constitute the lesions of what we call subacute and then chronic glomerulonephritis The glomeruli take on a more lobulated appearance with the capillary loops cellular and swollen and the basement membrane and wall of the capillary thickened (Figs 15 and 17) At points cap-



FIG 20 — Glomerulus showing more advanced stage of process shown in Fig 17 Now connective tissue has become increasingly acellular and hyaline

illary loops become adherent to Bowman s capsule with the cells about the former and those of the capsule proliferating and becoming continuous (Fig 18) Still later fibrils of connective tissue appear between the cells and increase in number while the cells undergo degeneration Also the few connective tissue fibrils normally in the stalk of the capillary tuft where the afferent and efferent blood vessels are increase in number thicken and extend out between the capillary loops to separate them more and more from each other all of these fibrils gradually thicken and shorten to exaggerate the lobulation of the glomerular tuft which now has decreased from its former swollen size and has an increased capsular

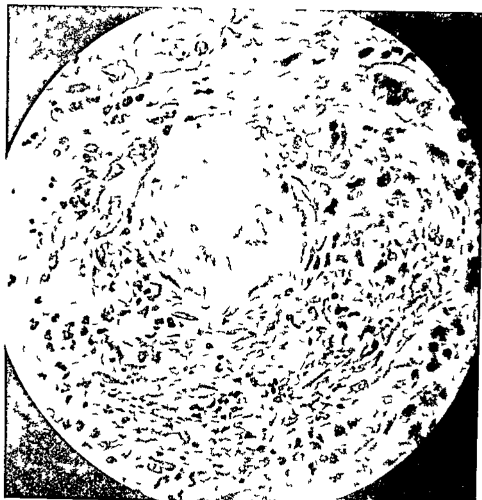


FIG 21 — Atrophied hyaline glomerulus

space about it while at the same time the proliferated endo and peri capillary cells begin to decrease in size undergo further degeneration and take on an hyaline appearance merging with the connective tissue which also becomes hyaline in appearance (Fig 19)

The proliferated cells of Bowman s capsule whether focal to form crescents or diffusely scattered, undergo similar changes with the appearance between them of fibrils of connective tissue while they like the cells of the capillary tuft degenerate and atrophy Adhesions between tuft and capsule often become more extensive Bowman s capsule also thickens and may become hyalinized Finally with these changes going on gradually glomeruli become shrunken hyalinized, avas

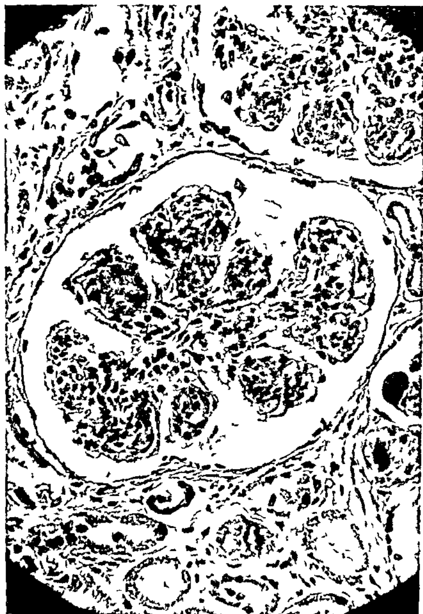


Fig 22 — Intracapillary glomerulosclerosis (Kimmelstiel Wilson lesion)

cular and fibrosed (Fig 21), and eventually many of them disappear so completely that no trace of them can be found

Since any or all of these glomerular lesions are found in a variety of conditions such as subacute bacterial endocarditis, acute or subacute pyelonephritis and experimental nephritis as well as in acute glomerulonephritis, they can not be considered specific lesions[138] The author[99] has described all of them in kidneys of patients dying from subacute *Streptococcus viridans* vegetative endocarditis and in kidneys of rabbits poisoned with uranium nitrate, in the former condition frequently being very numerous in the latter seen only occasionally, unless the uranium nitrate had been given intravenously or particularly when it has been introduced directly into the renal artery

It is to be remembered that the bulk of the blood going to the kidney passes through the glomeruli before it reaches the spaces between the tubules, that injurious substances in the circulation come in contact with the glomerular structures before reaching the intertubular spaces, and that lesions in the glomeruli, which hinder blood flow through glomerular capillaries, influence adversely the blood supply of the tubules So it is evident that lesions of the glomeruli will have an important relation to the condition of the tubules and the tissues between them This is shown in studies of renal function during the progression of the disease[803] On this account in glomerulonephritis there are tubular lesions, the cells lining the tubules showing varying degrees of swelling, granular fatty and hyaline degeneration and even necrosis and as time goes on, atrophy with or without dilatation of the lumen of the tubule As the glomerulus ceases to function the tubule usually dilates and becomes tortuous In the lumen degenerated tubule cells red blood cells and casts appear along with albumin, the latter in fixed stained sections of the kidney appearing as a granular detritus

In the earlier stages of glomerulonephritis the interstitial tissue may show only edema or possibly a few red blood cells In some the latter may become very numerous to form focal or even diffuse hemorrhages justifying for them the term, hemorrhagic nephritis Leucocytes lymphocytes and plasma cells may appear in the interstitial tissue later on this cellular infiltration is slight as a rule in acute nephritis but may be marked in subacute glomerulonephritis and the earlier stages of chronic glomerulonephritis With them appear also connective tissue cells with their characteristic nuclei In the later stages of chronic glomerulonephritis cellular infiltration decreases In the subacute and early chronic stages interstitial connective tissue increases and with chronicity it becomes more and more prominent to separate increasingly the tubules Later this often becomes cell poor and undergoes hyaline transformation

Occasionally in a patient dying of an acute infectious disease cellular infiltration, especially with lymphocytes and plasma cells may be marked and constitute

the chief renal lesion This is the *acute interstitial nephritis* of this classification of pathological lesions It was seen fairly often in patients dead of diphtheria or scarlet fever in my early experiences in the Laboratory of Pathology at the Boston City Hospital It causes no characteristic clinical picture

By *acute tubular nephritis* is meant a condition in which the cells lining the tubules show extensive degenerative changes granular fatty hyaline and are swollen and greatly reduce the lumen of the tubules Some or many of the cells may necrose Regeneration of these cells may take place and the regenerated cells show less differentiation of the nucleus and cytoplasm than was present in the original normal cells of the same portion of the tubule Sometimes a syncytium forms

These changes may occur along with glomerular and interstitial lesions particularly with the glomerular lesions of the nephrotic syndrome or may be the dominant lesion the latter strictly speaking constitutes acute tubular nephritis Such lesions of the cells of the tubules are very prominent in experimental nephritis[174 176], particularly that produced in rabbits by mercury bichloride and uranium nitrate the former may occur in man dead of mercury bichloride poisoning a not infrequent means to suicide When marked this lesion is the nephrosis of some pathologists and clinicians

Slighter degrees of degeneration of cells of the tubules occur in all of the acute infectious diseases but scarcely justify the term acute tubular nephritis clinically this is not considered to be a form of Bright s di ease

Vascular lesions in the kidney of acute type occur but since with one exception they interfere very little with blood flow and not at all with blood composition they do not cause appreciable change in extravascular renal structures or in renal function Consequently acute vascular nephritis is of very little importance in relation to Bright s disease

An exception to this lies in the hyaline change which occurs in the capillaries of the glomeruli already described in an early part of this section as acute hyaline capillary glomerulonephritis this may be the only glomerular lesion demonstrable in the kidney of patients dying with the nephrotic syndrome and so be of very considerable clinical importance

Chronic vascular nephritis the *chronic interstitial nephritis* of an older day is a frequently occurring form of chronic Bright s di ease The lesion in it of the renal blood vessels of all sizes is the same in histological appearance and in progression as that in blood vessels of similar size encountered in any of the body tissues as modified somewhat in each by the normal structure of their blood vessels The arrangement of the blood vessels which is found in the kidney particularly the facts that the bulk of the blood to the kidney passes first through the glomeruli and then to the region of the basement membrane of the tubules and that there are two capillary systems in the kidney the intraglomerular and the

intertubular, influence profoundly the effect of their structural changes on renal function

The vascular lesions in the kidney may be of a proliferative type, proliferative endarteritis proliferative mesarteritis, proliferative periarteritis, or of a degenerative sclerosing, sometimes necrosing type the latter affecting chiefly the media of the artery to cause a form of arteriosclerosis or arteriolosclerosis, depending on whether the arteries or the arterioles of the kidney chiefly are involved Since the small vessels in the kidney the arterioles are the ones, which, when pathological chiefly influence renal function, the chronic vascular lesion of the kidney usually is spoken of as arteriolonephrosclerosis, the most frequent form of chronic vascular nephritis

Of the vascular lesions those of the arterioles, afferent and efferent, of the glomeruli are of particular importance particularly when the lesion is of a nature, chiefly endarterial to decrease the lumen of the arteriole and probably, along with mesarterial change, to hinder its physiological contraction and dilatation Occasionally in these arterioles thrombi will form and organize to impinge further on the lumen of the vessel (Fig 16) Lesions of these same types occur also in the arteries from which arise the afferent arterioles of the glomeruli Lesions in this vascular system of the kidney must influence profoundly the flow of blood through the glomeruli and indirectly into the intertubular vascular system, where too the same sorts of lesions are found to influence further the blood supply to the renal tubules

Just as is true of glomerular lesions the vascular lesions are, as a rule, diffuse in distribution with numerous variations in the single kidney of the observed histological changes but often with some particular one dominating the picture Focal vascular lesions do however occur

With the presence of vascular lesions naturally go degenerative changes in both the cellular and interstitial structures supplied by these blood vessels, and these lead to tubular and glomerular atrophy and interstitial fibrosis resulting in a small kidney Since sclerosis and atrophy is more prominent in certain areas than others and occurs more in the cortex than in the medulla of the kidney, the resultant kidney is small and granular and being relatively vascular is red, *in the gross* the small red granular kidney in contrast to the small pale, less granular kidney of chronic glomerulonephritis

Subacute and *chronic pyelonephritis* have been included in the pathological classification of Bright s disease while acute pyelonephritis has not, the latter being considered as a form of inflammation of the kidney of bacterial etiology with the symptomatology of an acute infection Possibly the subacute form also preferably might be grouped since often the clinical picture is that of prolonged or repeated bacterial infection of the kidney On the other hand, as time goes

on and a chronic stage is approached the features included in the definition of Bright s disease given at the beginning of this chapter begin to appear and very often in the chronic stage it is difficult to distinguish chronic pyelonephritis from other typical forms of chronic Bright s disease

Pathologically the kidney of subacute and chronic pyelonephritis shows a variety of lesions involving all renal structures glomeruli tubules blood vessels and interstitial tissue[139] It has been well said that in certain of these kidneys a single section may show every lesion that has been described in the kidney of any form of Bright s disease To save repetition it can be said here that in subacute and chronic pyelonephritis any of the lesions described up to this point in this section on Pathology may be found What distinguishes pyelonephritis in its pathology from the several forms of Bright s disease is found in the interstitial tissue namely the cellular exudation of an inflammatory process accompanied by a progressively increasing fibrosis as occurs in the organization of acute exu dates Leucocytes progressively decrease leaving lymphocytes and plasma cells which in turn decrease so that eventually the collagen fibrils and fibres between the tubules and about the glomeruli as they increase in amount are less and less infiltrated with cells and the connective tissue cells at first numerous decrease in number i e the interstitial tissue gradually becomes a cell poor connective tissue in a kidney which has been shrunken in size during this proces to become even tually a small rather smooth or somewhat coarsely lobulated pale kidney whose pelvis often is a thickened chronically inflamed structure

Kimmelstiel and Wilson[140] described a lesion *intercapillary glomerulosclerosis* which they considered specific for a clinical syndrome of diabetes mellitus hyper tension edema of renal origin and not infrequently uremia This is an increase in connective tissue outside the capillary tufts of the glomeruli sometimes diffuse more often focal in one or several intercapillary areas[138 140] with it goes changes in the tubules and interstitial tissue as in other varieties of glomerulonephritis in addi tion to slighter vascular lesions of arteriolonephrosclerosis (Fig 22) The lesion usually is spherical sometimes oval and is made up of faintly acidophilic acellular hyalinized tissue Under low magnification the lesion seems homogeneous but with higher magnification small vacuoles are seen At the periphery usually there are flattened endothelial like cells to form a layer of one or more cells There may be only one or several of these lesions in a glomerulus and the involved glomeruli may be few or very numerous in sections of the kidney In the glo meruli instead of the lesion just described there may appear about and between the capillaries of the loop linear fibroses hyaline in appearance as if the capillary wall in places had greatly thickened and undergone hyaline transformation Some glomeruli as a result of this become extensively fibrosed Both types of lesion appear at times in the same glomerulus Kimmelstiel and Wilson[140] be lieved that these lesions developed from hyalinization of the intercapillary con

nective tissue of the glomerulus Some of them look more as if they had developed by local thickening and hyalinization of the basement membrane of the capillary loop This lesion occurs in the clinical syndrome[141] noted above, but it is not specific for it since it has been described in patients not having the clinical syndrome of Kimmelstiel and Wilson and even in some diabetic patients not having any of its features

These lesions are very frequent in diabetics particularly diabetics of the older age groups but they are found also, although very infrequently in young diabetics Some observers[177] regard them, if lesser development of them is included, as of such frequency as to be the best morphological evidence we possess that the patient during life has had bad diabetes mellitus However, identical lesions do occur in patients who have had no diabetes, particularly patients with renal arteriolosclerosis and sometimes in patients with glomerulonephritis or with subacute or chronic pyelonephritis I have seen scattered, occasional typical lesions of this type in kidneys of patients dying from *Streptococcus viridans* subacute endocarditis Consequently intercapillary glomerulosclerosis can not be said to be pathognomonic of diabetes mellitus and in the diabetic they occur in the absence during life of the Kimmelstiel Wilson syndrome, which is discussed in Part II

A very infrequent lesion is *cortical necrosis of the kidney* caused by a particular circulatory blockage Almost always the lesion is bilateral It seems to occur most often in connection with toxemia of pregnancy but it occurs also but with less frequency in patients severely ill with an infectious disease and after trauma Rarely it has seemed to have no antecedent illness With its greatest frequency in pregnancy women preponderate considerably over men Duff and More[182] in an excellent review of 71 cases found 48 occurred in pregnant women 8 in non pregnant women and 15 in men and in ages 13 to 64 In this lesion blood flow in intralobular arteries is blocked causing large areas of the cortex to show a greasy yellowish appearance from necrosis with small scattered hemorrhagic foci in them and often an hemorrhagic border zone or there are smaller scattered areas of the same appearance in the cortex The columns of Bertini usually are involved, but the pyramids are spared Microscopically renal cells show ischemic necrosis and blood vessels may or may not contain thrombi The fundamental lesion according to a few seems to be a degeneration of the wall of the afferent arteriole as it enters the glomerulus with local thrombosis extending retrogradely to cause multiple infarctions which rapidly coalesce More observers consider the cause to be diffuse thrombosis of the intralobular arteries due either to a diffuse degenerative lesion of the arterial wall causing thrombus formation or to some form of thrombus formation leading secondarily to lesions of the arteries from resultant anemia Still others believe the first change is ischemia from prolonged vasospasm in blood vessels for some reason hypersensitive in their reactions Almost all seem

to agree that cortical necrosis is the result of obstructive ischemia. Areas of necrosis may be found occasionally also in other organs. Of particular interest has been an associated necrotic lesion of the pituitary[353, 354]. This has suggested to some observers an endocrine disturbance as a factor in cause of the lesion. The lesion has been produced experimentally in animals by a diet deficient in choline[3, 6], by intravenous staphylococcus toxin, by intravenous injection of lithium carbonate[109] and of vasopressin.

In bilateral papillary necrosis dirty yellowish gray papillae stand out in striking contrast to other parts of the kidney. Sometimes all, sometimes only the tip of a papilla shows the necrosis. Sometimes a few, sometimes many, sometimes all of the papillae are involved. Sequestration of papillae may occur. Necrosis of the tissue of the papillae may be present with few or almost no cellular exudate, or there may be infiltration with many cells, leucocytes, plasma cells, lymphocytes or eosinophils in varying proportion. These kidneys show pyelitis and different degrees of pyelonephritis.

In a group of clinical conditions[391–396] with such varied names as *shock, traumatic uremia, crush syndrome, myolobinuria, hemoglobinuria, transfusion reaction, blackwater fever, sulfonamide kidney*, etc., the pathological lesion is in many ways very similar. In all of these the kidneys are swollen, degenerative changes in the epithelium of the tubules usually are prominent, varying from granular or fatty degeneration to cell necrosis. With necrosis leucocytic infiltration occurs. The glomeruli usually are bloodless, sometimes but not often they show changes already described for various forms of glomerulonephritis. In some of these kidneys deposits of heme pigments, derivatives of myoglobin or hemoglobin are added features, being present both in cells and obstructing glomerular spaces and tubules.

In sulfonamide toxicity crystals of the drug and concretions often block tubules. Focal destruction of the tubules takes place where crystals are precipitated. About crystals hyaline material appears with round cell infiltration and hemorrhage about it[400], sometimes giant cells[412]. The epithelium lining tubules usually shows diffusely granular degeneration with some cells necrotic. In some necrosis is prominent. In some patients there are marked necrotic changes in the pyramids. Sometimes in kidneys from patients with these clinical syndromes cortical necrosis, as already described, develops.

In the *hepatorenal syndrome*[396, 417–421] the kidney and liver both show degenerative changes. In some patients kidneys show only slight degenerative changes in the tubular epithelium, not enough to explain satisfactorily their insufficiency in life. In others the epithelium shows quite extensive degeneration, sometimes with necrosis. In a few cases epithelial necrosis is extensive. With liver damage often there are added the pathological features which accompany jaundice. The syndrome has occurred following biliary, hepatic, thyroid and gastrointestinal

tract surgery, in various forms of severe sepsis and infectious diseases, after burns and after poisoning with such substances as heavy metals, chloroform, cinchophen, dioxane, diethylene glycol and carbon tetrachloride. One view is that liver injury produces toxic substances or the injured liver loses its detoxifying function, and that these toxic substances cause then the kidney damage. The other view is that the underlying disease causes simultaneously degenerative lesions in kidney and liver. Swelling of the kidney also may play a causative part.

In *amyloidosis of the kidney*[397, 398] amyloid is deposited chiefly, possibly first, in the walls of the capillaries of the glomeruli and the arterioles afferent and efferent to the glomeruli, later in the walls of the intertubular capillaries and arterioles and in the intertubular connective tissue, especially in the basement membrane of the tubules. Gradually amyloid encroaches more and more on the glomerular structure and finally less or more completely replaces it with obliteration of the glomerular space. Some tubules show atrophy, others hypertrophy. Size of the kidney varies greatly. In some patients the kidneys are larger than normal, pale gray or yellowish, sometimes edematous, in others the kidneys are of normal or slightly smaller than normal size. These kidneys are smooth. More often the kidneys are smaller than normal, not so pale, somewhat lobular with adherent capsules. In these connective tissue is increased, and arteries and arterioles show sclerosis as in vascular nephritis. It is uncertain whether these last changes are the result of the amyloid deposition, or whether the amyloid is deposited coincidentally in kidneys developing the lesions of vascular nephritis. Almost always amyloidosis is not restricted to kidneys but is present in other organs, especially in the spleen and liver.

In *myeloma kidney* the disturbed renal function is due to the mechanical blocking of tubules by deposited Bence Jones protein to a degree to interfere with excretion of urine. Sections of the kidney show these deposits as casts in tubules with dilated lumens lined by low, i.e. atrophied, epithelium. Sometimes they act as foreign bodies, and giant cells form about them.

Cysts develop often in the kidney. In many patients with chronic Bright's disease kidneys, usually smaller than normal, often focally or generally fibrosed, show scattered cysts of small or medium size; they have little or no effect on the disease process. Occasionally large cysts, as a rule single or solitary, most often at the lower pole of the kidney, appear in kidneys otherwise normal. These may be large enough to present as abdominal tumors or even cause intestinal obstruction or other pressure phenomena. Not infrequently many small cysts develop in the kidneys early in life and gradually increase in size and compress renal tissue between the cysts so as to hinder its normal excretory function; there results later in life bilateral cystic renal tumors, so called *polycystic kidneys*. These cysts almost always are in the cortex, very rarely they are in the pyramids of the kidney. In an occasional patient the cysts are not very numerous and do

not, as they develop hinder renal function In some of the patients with this form of cystic disease, cysts appear also in other structures liver pancreas lungs

Practically all kidney cysts have smooth thin walls lined by greatly flattened cells and contain a thin serous or mucoid fluid unless hemorrhage into them as is not infrequent has taken place or they become infected as they may, and the contents becomes purulent In a cyst wall sometimes calcium is deposited or a blood clot in it becomes partly calcified

Cysts that develop in kidneys with the lesions of chronic Bright s disease seem to develop because a glomerulus becomes constricted at its point of contact with a tubule or a tubule at some point becomes constricted and continued ex cretion of fluid causes dilatation eventually to form a small thin walled cyst its lining epithelial cells having lost all resemblance to the original renal epithelium

The other forms of cysts are believed to have resulted from an anomaly in development by which different portions of kidney tubules fail in embryonic life to connect with each other in the normal way These cysts are generally believed to be of congenital origin but some do consider them as a form of neoplasia

Hypoplasia, unilateral or bilateral may be found due to congenital anomaly in renal development or due to an anomaly in the development of the blood supply of the kidney The latter may be the cause of the former change

Heart

In Bright s disease the chief pathological change found in the heart is hyper trophy with increase in weight and in thickness of the wall of the various cavi ties[142] Heart hypertrophy was described by Bright in 1827[1] These changes take place first in the myocardium of the left ventricle later in that of the right ventricle and the auricles In acute Bright s disease cardiac hypertrophy of slight to moderate degree may develop infrequently it becomes marked in acute Bright s disease, others believe it occurs with great frequency in chronic Bright s disease hypertrophy is the rule although in some patients notably those with extensive edema the nephrosis syndrome it appears only late in the progression of the disea e Very often the heart in chronic Bright s disease becomes very large and eventually cardiac decompensation ensues These cardiac changes are associated usually with high blood pres ure[147]

Histologically the chief abnormality in the heart lies in the increase in size of the muscle fibers without any increase in the number of the capillaries[143–146] Sometimes the muscle fibers show slight degenerative changes and there appear small foci of increase in interstitial connective tissue the latter being only mod erately cellular with slight infiltration with lymphocytes and fewer plasma cells muscle cells in and about these foci may show loss of striations atrophy or com plete disappearance

The coronary arteries in these hearts often show arteriosclerosis of patchy distribution in the larger branches and more diffuse in the smaller branches The very small arteries and arterioles very frequently show diffuse thickening of the wall with hyaline degeneration and endothelial proliferation especially in those patients in whom blood pressure, particularly the diastolic pressure, for a long time has been high or has risen rapidly and persisted at a high level for a few months, lesions like those seen in essential hypertension of the so called malignant type

The chief cause of the pathological changes in the myocardium in Bright's disease is the coincidental hypertension discussed under the general heading Pathological Physiology In addition the frequent arteriosclerotic and less frequent arteriolosclerotic lesions of the coronary system in all probability play some causative role in the myocardial lesions In the acute cases there is too, a possible effect of toxic substances, acting directly on the myocardium or indirectly as an allergen, in these patients streptococci often have an etiological relation and may be productive of circulating toxins

In the terminal stages of Bright's disease usually in association with uremic symptoms an *acute fibrinous pericarditis* develops This is believed to be a chemical inflammation associated with an unknown component from renal retention or to result from arteriolar lesions in the pericardium Some consider however that deposited urea brings about a necrotic change in the superficial layers of the pericardium and this causes the fibrinous exudation This pericarditis is not of infectious etiology By some it is called *pericarditis uremica*

Blood Vessels

A sharp distinction needs to be drawn between changes in the large and the small blood vessels. As large blood vessels we think of arteries which when in the subcutaneous tissue are of a size to be felt by the palpating finger and veins when similarly situated large enough to be visible. Failure to make this distinction leads to a frequent clinical confusion between the changes of hypertension and of arteriosclerosis, two processes whose cause and significance seem definitely to be different. Both are frequent in chronic Bright's disease.

In a clinical sense it seems best to regard as arteriosclerosis changes in the larger arteries consisting of irregular thickening of the walls of the vessels with a frequent incidence of calcification. Such arteries often seem relatively large, have a beaded feel and frequently are tortuous. With marked calcification they are called pipe stem arteries. The x ray will reveal calcification either focal or diffuse in these arteries and their minor branches. The x ray will show a widened and often tortuous thoracic aorta, particularly when there is hypertension as well as arteriosclerotic changes, often with local calcification in the aorta. This usually is distinguishable from the bulging localized in the first part of the aortic arch which is characteristic of syphilitic aortitis. Fluoroscopy always adds valuable data to that obtained from a study of the x ray film.

Very many of these patients with arteriosclerosis have a low normal or only moderately heightened blood pressure and a normal or decreased pulse pressure. The radial pulses are of moderate size, tending to a rather gradual fall and rise of the pulse with a rounded top to the pulse wave, and the artery wall is irregularly thickened, "beaded," rather than diffusely uniformly thickened. Students constantly confuse these changes with those of hypertension and express surprise when they do not find the manometer showing a high systolic pressure, or feeling the pulse, state that they think the blood pressure will be high. They confuse the resistance of the vessel wall with an increased intravascular tension, not differentiating the sensation obtained by the palpating finger when the blood current is obliterated by pressure of another finger at a higher or more proximal level, as usually, but not always, can be done.

Sir Clifford Allbutt's differentiation between arteriosclerotic or decrescent[148] changes in vessels and those of hypertension or hyperpiesis holds good still and is very valuable in clinical use because there is no doubt but that the arteriosclerotic changes without high blood pressure, as described above, fit in clinically with the idea of a degenerative change of some sort going on. They are found in the old or prematurely old, and the patient's general appearance usually corresponds with his vascular condition, i.e., the possessor of these vessels looks old. With such arteriosclerotic changes as a rule there are evidences of a moderate dis

turbance in the kidney, a little albumin, a few casts slight lowering of renal function changes which increase as arteriosclerotic lesions increase

Often in sharp contrast to these arteriosclerotic lesions in larger vessels without increased blood pressure are the findings in the larger vessels in patients with hypertension Quite often the arteries feel almost normal, but usually there is the sensation of increased tension It is to be emphasized that the palpating finger is not a sure judge of blood pressure, and reliance can be placed only on instrumental determination of blood pressure Still the vessel often seems full, although its calibre may be small It is difficult to obliterate the pulse at a lower level by pressure at a higher Frequently the pulse wave has a quick rise and fall Pulse pressure often is increased and there may be vigorous pulsation along with visible capillary pulsation in the finger nails as in the Corrigan pulse of aortic insufficiency Not infrequently the artery is lengthened so that it is tortuous as well as dilated The thoracic aorta may show this by x ray The vessel wall may be thickened but this is not a patchy thickening, and there is no calcification in the earlier stages Later with hypertension arteriosclerotic changes, as described in the previous paragraphs usually appear very likely, although not certainly, the result of the effects on the arteries of the continued high blood pressure With a failing heart pulsus alternans and various arrythmias appear Such vascular findings very often are encountered in the patient with Bright's disease especially chronic Bright's disease but in many patients with hypertension there is little or no evidence of renal lesion

If the processes remained separated there would be very little difficulty, but so often both changes are found in the same individual Most observers now think that in patients with hypertension the arteriosclerotic lesion results from the hypertension, which is not true in the non hypertensives It seems better to regard the two conditions as different although often occurring in the same individual Observations by means of the x ray on diabetics with hypertension in contrast to non diabetics with hypertension show a striking preponderance of calcification in the first group indicating that the diabetes rather than the hypertension in some way is responsible for the calcification This suggests again that hypertension and the form of arteriosclerosis with calcification are different processes, even though the former at times causes the latter

Larger veins frequently show thickening of the wall phlebosclerosis like the arteries in arteriosclerosis but these changes have, so far as is known, little clinical significance

When we come to smaller arteries arterioles, capillaries and small venules far less definite knowledge is at hand In the histological study of tissues from some patients the smaller vessels everywhere seem to have narrowed lumens and thickened walls Hyaline degeneration in the vessel wall is very frequent The elastic

tissue is increased appearing as branching and reduplicated layers sometimes with evidence of degeneration Endothelium may proliferate The lumens of small arteries, as a rule seem narrowed In the gross these vessels stand out prominently in the cut surfaces of the tissues During life the eye grounds of patients with hypertension show lesions of the small vessels as described later under Eye in a large percentage of cases Somewhat similar changes are seen in the vascular tufts of the skin papillae when viewed by oblique illumination under the microscope after oil is dropped on the skin at the base of the finger nail However all of these changes may be lacking at times in patients with high blood pressure After all the technique usually applied to the study of autopsy material is unsatisfactory for the minute study of the small blood vessels and we must await better methods before we will be in a position to say much in any positive way about the presence or absence of organic changes in the very small vessels of the body in general Yet it is in these small vessels that the cause for hypertension lies according to the commonly accepted theory

As to capillaries, we know even less Recent physiological investigation has shown that they play a far more active part in the circulation than was formerly thought but their pathology as yet remains unwritten We know that there is a far richer capillary supply in most tissues than appears in sections stained for histological study as is shown by injection methods and by vital staining but to human pathological material such methods have been little applied owing to technical difficulties inherent in the material and it may be that changes in capillaries are entirely functional rather than structural

*Even admitting all of these deficiencies in our knowledge of blood vessel dis*turbances there remains enough to show that vascular lesions either structural or functional, have a very important role in our patients with Bright s disease and they have to be taken into consideration whenever we attempt to study understandingly this disease, even if these changes are caused indirectly by the Bright s disease as probably is the case

Eye

Pathological changes in the eye occur frequently in Bright s disease especially in any form associated with continued high blood pressure The optic nerve head and the retina in particular show lesions The effects of these in dimming vision was noted by Bright in his monograph of 1836 Since these changes are visible with the ophthalmoscope the use of this instrument is essential to the clinician in following the course of Bright s disease in his patients Fortunately with modern instruments ophthalmoscopy is not difficult and since it gives valuable information also in various diseases other than Bright s disease every physi

cian should know how to use the ophthalmoscope and apply it as regular routine in his examination of his patients

For many years the chief pathological lesion in the eye of patients with Bright s disease has been called albuminuric retinitis, a term introduced in 1859 by Liebreich[14] The first ophthalmoscopic observation and description of observed changes are attributed to Heymann in 1858[1 0] As knowledge of these lesions has increased, this term has come to be a less and less appropriate name for the process It implies that it is an inflammation based on, or caused by, albuminuria whereas it is neither inflammation nor directly related to albuminuria, in that form of Bright s disease, the nephrosis syndrome, in which albuminuria is most marked, these retinal lesions are very infrequent and they may occur in patients who do not show any albuminuria Hypertensive retinopathy or hypertensive neuroretinopathy is a suggested term the words meaning a pathological lesion caused by or at least associated with hypertension, a term analogous to hypertensive encephalopathy[1 1] This term, hypertensive retinopathy or neuroretinopathy, however should not be used strictly speaking, in the infrequent patient, who without having hypertension shows the same ophthalmoscopic appearances or at least very similar appearances For this reason some use two terms, hypertensive retinopathy and arteriosclerotic retinopathy but this brings confusion rather than clarity for many do not think the two processes are always distinguishable Some still attempt to distinguish two processes hypertensive retinitis and albuminuric retinitis or retinopathy using the second term for cases in which they regard the retinal lesion as of toxic origin a manifestation of uremia caused by renal retention Retinopathy is a term used by some, it has the advantage of including any lesion seen in the retina but will require some added descriptive term to separate out the lesions observed in the retina of patients with Bright s disease from a variety of lesions in the retina of other associations Ophthalmopathy is used, too this has the advantage of including changes that occur in the nerve head but brings the disadvantage of including any lesion of any cause in any part of the eye The dilemma of terminology of late has been met in two ways some retain the old term albuminuric retinitis understanding that it is a term which nowadays is used with the understanding that the lesion so called is neither a retinitis nor albuminuric others use one of the other terms just discussed or none of these terms, merely stating as a descriptive terminology the presence of hemorrhages, white spots papilledema retinal edema and variations in the appearance of the retinal blood vessels Now for many years this has been the practice of the author of this chapter At present the theory of a vascular basis for these changes seems adequate without the aid of hypothetical toxins a toxic effect remains as a possibility in explanation of part of the changes, although not believed in now by most students of the subject

For an understanding of the changes which occur in the eyes of patients with Bright s disease, certain anatomical peculiarities of the blood vessels of the optic nerve and retina need to be recognized These are described very well by J S Friedenwald[15] of Baltimore from whom I will quote extensively

The retinal artery in its course through the orbit and optic nerve has a relatively thick muscular coat similar to that of other vessels of similar size but on passing through the cribriform plate into the eye the arterial coat abruptly dwindles to about one third its previous thickness The intima remains unchanged the elastic lamella is at first preserved somewhat reduced in density but disappears from the secondary or tertiary arterial branches in the retina the adventitia becomes thinner and looser in structure The greatest change in the vessel on entering the eye is in the media, which becomes reduced to a thin layer usually less than one tenth the diameter of the vessel in thickness It is difficult to demonstrate histologically the presence of smooth muscle fibers in the media of the retinal arterial branches That contractile elements are present is undoubted on clinical and experimental grounds On account of the thinness of the retinal arterial walls and their considerable variation under normal conditions and also on account of the difficulty of estimating the functional internal diameter of collapsed retinal vessels seen in microscopic sections minor changes in thickness of the arterial walls are difficult to recognize on microscopic examination In the larger arterial branches in the retina the intima is sufficiently developed to allow atheromatous degeneration similar to the changes in larger arteries in arteriosclerosis These vessels also may show hyaline degeneration of the media characteristic of arteriosclerosis It is of no interest whether these vessels are arteries or arterioles The important fact is that they are capable of partaking differently in two different disease processes of the vascular tree and that therefore the careful clinical study of these different forms of vascular degeneration in the retina is of importance diagnostically and prognostically

A further peculiarity of the retinal vascular tree is the crossing of the retinal arteries and veins The retinal vessels excepting only the finest twigs and capillaries are spread out in a two dimensional plane with the result that the arteries and veins are brought into intimate contact with one another at points of crossing In other organs the large arteries and veins often lie in a common sheath *like the central retinal vessels in the optic nerve while the smaller twigs* of the arteries and veins branch apart and have no connection with one another except through the capillaries An exception to this rule outside of the retina is found in the afferent and efferent vessels of the kidney glomerulus Whether this fact is significant in the physiology and pathology of the kidney the author leaves to other participants in this volume

The histology of the retinal arteriovenous crossings has been studied care-

fully by Koyanagi[1 7] At the points of crossing the vessels have a common adventitia which surrounds them without extending into their wall of contact Here the media of the artery is in direct contact with the inner layers of connective tissue of the venous wall so that it becomes impossible to say where one begins and the other ends The total thickness of this common wall is not significantly greater than the arterial wall alone at other points The consequences of this intimate binding together of arteries and veins will be discussed in regard to the so called arteriovenous constriction and in regard to venous sclerosis"

Friedenwald[1] also has summarized in another place in the same chapter the changes observed in the eye in Bright's disease as follows (1) vascular changes, beading of the vessels or localized variations in caliber, general constriction or dilatation of the arteries, arteriovenous constriction increased visibility of the vessel walls, copper wire and silver wire vessels arteriolar occlusion and changes in the light reflex over the vessel (2) retinal changes edema of retina and optic disc serous fibrinous and hemorrhagic extravasations in the retina, cytoid bodies in the nerve fiber layer flat serous detachment of the retina, arteriolar occlusion and retinal infarction and secondary and reparative processes as lipoid, especially cholesterol deposits about the retinal vessels, fat droplet cells, scarring of the retina with glial proliferation and cystic degeneration Vascular changes are believed to be due in part to spasm of the vessel, in part to organic change in its wall spasm probably precedes organic change Some believe spasm causes the organic change most believe that organic change often appears without, or independent of antecedent spasm There is some evidence that proteolytic enzymes play a causative role in the organic lesions in blood vessels and retina and their activity is related to the anoxemia from local arteriolar spasm (cited by Friedenwald[15]) The exact relationships remain problematical, but there is general agreement that the changes in the eye in Bright's disease are, for the most part of vascular and not inflammatory origin degenerative rather than infiltrative lesions

The changes in the eye just described are responsible for the ophthalmoscopic appearances connoted by the terms hemorrhages white spots, papilledema, retinal edema and variations in the appearance of the blood vessels

In that group of cases that immediately concerns us those with Bright's disease, search should be made for abnormalities in the disc or nerve head the retina and the retinal vessels The variations that occur in the disc are of three kinds papilledema hemorrhage and increased vascularity While certain authors mention truly choked disc as occurring in Bright's disease, it seems that it is a distinct rarity The lesser forms of papilledema, however, are fairly common especially in late chronic Bright's disease Almost always the condition is bilateral, although it may be unilateral shortly after a cerebral hemorrhage On these

occasions this disc swelling often is on the side corresponding to the brain lesion The finding of this unilateral papilledema is not at all constant, however, in cases of cerebral hemorrhage

It is in the serious type of cases that hemorrhages into the nerve head sometimes are associated with the papilledema These usually are lancinate and run off the disk into the surrounding edematous retina The other abnormality of the nerve head to look for is far less common and is seen only occasionally in a well marked state This is the increased vascularity of the disc which is one of the evidences of arteriosclerosis This means an increase in the visible small vessels in the optic nerve In a rare case of vascular disease this may take a bizarre form with twisting closely packed small vessels radiating off the disc like wriggling snakes to produce a complete or partial caput Medusae Closely related to this increased vascularity is the congestive redness occasionally seen

In the patients showing papilledema usually there is edema of the surrounding retina and also in the macular region recognized easily by the general cloudiness and the lack of definition in the vessels running through these areas Edema of the other parts of the retina undoubtedly occurs but it is recognized rarely in its early formation except around the disc in conjunction with papilledema or when it has caused a localized detachment of the retina often with the later appearance of cyst like spaces in the retina Later the edema fluid becomes more concentrated and richer in protein, especially fibrin and it appears as a fuzzy grayish area so called cotton wool spots or areas These appearances may involve a large part of the central half or two thirds of the retina If lipoid substances accumulate in the fluid the color becomes white or yellowish In certain areas of the retina this causes the formation of rounded clots or radiating lines as in the star about the macula

Hemorrhages in the retina as they occur in Bright s disease and vascular disease may be single or multiple of various sizes and shapes and may be placed anywhere The round hemorrhages are in the deeper layers the flame shaped and linear hemorrhages are more superficial The latter types are the more common Occasionally one sees the stippled hemorrhage which consists of a group of closely packed faint, punctate hemorrhages Very rarely is the large boat shaped subhyaloid hemorrhage seen Although the hemorrhages may be seen anywhere in the retina, they are more common on the temporal side about 1 to 2 papillary diameters from the disk

The superficial hemorrhages may disappear in a few weeks The deeper and larger ones may last for many months If they involve the very deep layers as they absorb they may leave areas of brown or black pigment Usually these hemorrhages become smaller and fade out without much change during the process other than a slight darkening Sometimes the hemorrhage fades leaving

a white spot, which in turn fades and disappears According to Moore[154] hemorrhages may occur in apparently healthy people and in those that are seriously ill from any cause as well as in the well recognized associations such as in pernicious anemia, leukemia, diabetes and vascular disease If this is so, the finding of a retinal hemorrhage may, in itself, be of no particular importance We know, too that even in hypertension one may find hemorrhages in the retina that cannot be of any great prognostic value In a vascular hypertensive patient several hemorrhagic spots were seen in her eyes Ten years previously the same patient had hypertension with a retinal hemorrhage On the other hand one cannot help feeling that the presence of retinal hemorrhages adds a bit to the likelihood of cerebral hemorrhage in those patients that have considerable retinal arteriosclerosis and a high diastolic pressure

When we come to the white spots, which are found so frequently in the retina, we are dealing with a lesion about whose origin there is a considerable difference of opinion These white spots as one sees them through the ophthalmoscope, are extremely varied in appearance They range in size from the very minute spot that is hard to distinguish from the surrounding retina to the huge homogeneous or coalescent areas that practically fill the posterior part of the eye ground In color they vary from grey through buff to a clear bluish white Some of these variations are due to differences in their pathology Some originate from changes in the fluid of retinal edema as already discussed The spots may be due according to Adam[155] to "connective tissue proliferation of the glia, to varicose thickening of the layer of nerve fibers to fatty degeneration to edema to fibrinous or serous exudates, to deposits of calcareous matter or to hyaline degeneration" Fatty degeneration "is certainly the principal cause of the white spots To it are to be ascribed the white spots ordinarily to be seen in albuminuric retinitis [155] This same author feels that the so called macular star or fan, which is so striking a figure in some patients, is due to fatty degeneration Moore[154] states however that it is of a hyaline type Others think it results from lipoid deposits in receding edema fluid and takes this arrangement because of the anatomical structure of the retina about the macula This figure and the so called cotton wool exudate are the two most important types of white spots that are concerned in this discussion The cotton wool patch is of fibrinous nature and is particularly characteristic of the subacute or subchronic type of Bright's disease In some cases these spots are so thick that they almost obliterate the normal red over a large portion of the posterior part of the globe The cotton wool white spots not infrequently fade and eventually disappear This lesion is regarded by many as a toxic effect according to Moore[154] and to Benedict[156] this is even true when it appears in patients with hypertension Others, as Friedenwald[157] and Verwey[158] think it is associated with, even if not caused by, arteriolar sclerosis

of the retinal vessels in which are seen numerous atheromatous plaques best demonstrated with fat stains in preparations made by spreading out the retina on a slide rather than by cutting sections (Friedenwald[1])

There are two other abnormalities in the retina that are worthy of brief mention Separation of the retina does occur in chronic nephritis especially where the other retinal changes are marked It seems to be a distinct rarity Atrophy of the retina is especially important in those cases of chorioretinitis affecting the macular region A lesion of this type even when small may cut down the vision quite markedly, whereas fairly extensive hemorrhages or white spots by comparison affect the vision only slightly as the latter are in layers other than those of the visual cells Such atrophy fortunately is not very common

One should remember, however that errors of refraction may be present and contribute largely to the poor vision in eyes that show these various retinal changes If these are corrected by proper glasses considerable improvement in vision may result which is very gratifying to the patient Consequently with evidences of refractive errors in these patients it is worth while to have proper glasses adjusted to see what improvement in vision may be brought about

The only element remaining for consideration is the vascular change in the retina that may take place in Bright s disease and allied disorders The changes in the arteries indicating arteriosclerosis are many and varied Abnormal tortuosity especially the corkscrew small vessels broadening of the central light streak lateral streaking straightening and stiffening general narrowing, silver wire and copper wire arteries resulting from lipoid deposits and hyaline change in the vessel walls respectively so called arteriovenous constrictions where an artery crosses a vein irregularities, unevenness or pinching of the lumen of vessels replacement in part or in whole of the red line by a white line indicating that the normally transparent wall has become opaque, are the chief features to look for Sometimes arterial thrombosis is seen or more often venous thrombosis Arteriovenous constrictions are among the most significant changes observed with the ophthalmoscope As already stated these are not simply places where a small artery crosses a vein but at these points actually the walls of the artery and vein are continuous structures so that between artery and vein there is no separation in to wall of artery and wall of vein and the thickness of the structure between the lumens of each vessel is not significantly greater than of the arterial wall alone beyond the point of crossing With this knowledge it is obvious that constriction of the vein at the point of crossing may be produced in several ways as has been stated by Friedenwald[15] 1 If the artery is displaced as a result of increased or decreased tortuosity it must drag the vein with it and if the drag is sufficient produce a constriction at the crossing This perhaps ought to be spoken of as arteriovenous displacement It occurs in conditions in which the tortuosity of

the arteries has recently been increased, and in the cases of shrinkage of the arterial tree mentioned above It has been credited as a sign of hypertension, though in fact it may occur without change in the blood pressure No histological changes are associated with arteriovenous displacement, unless marked venous stasis is produced

' 2 If the arterial wall becomes thickened and its external diameter increased, it must encroach upon the space within the common arteriovenous adventitia and constrict the lumen of the veins Such conditions are found in cases of retinal arteriosclerosis when in addition to atheromatous plaques of the intima, a fibrous thickening of the media and adventitia is present This need not be associated with hypertension or renal disease but is due to retinal arteriosclerosis More commonly the thickening of the vessel wall is due to arteriolosclerotic thickening of the media with hyaline degeneration This is invariably associated with hypertension and sooner or later complicated by renal disease The condition can be recognized ophthalmoscopically, when the vein is seen to curve sharply around the artery without necessarily being displaced laterally in its course

3 Owing to the fact that the arteriovenous wall is a single indivisible structure sclerotic changes in the artery may extend into the vein, sometimes reaching up and down the vein for a short distance from the crossing This accounts for the extraordinary frequency of retinal venous sclerosis and thrombosis Veins of this size in other organs show such lesions only with the greatest rarity Ophthalmoscopically this sclerosis of the retinal veins can be recognized by a narrowing of the venous blood column for a short distance on either side of the crossing "

The changes in the veins apart from the dilatation that occurs in papilledema, the narrowing at arteriovenous crossings and unevenness of calibre, are scarcely worthy of mention As a matter of fact changes in the veins are for the most part ignored because we concentrate our attention on the arteries Perhaps we might learn more, if we paid greater attention to the veins

The average internist will do well to stick to those signs that are absolute Such are compression effects at the arteriovenous crossings with narrowing of the vein unevenness of calibre and the replacement of the red column by the white line

The condition of the retinal vessels is a most important prognostic sign, forming, as it does an index of the condition of the small cerebral vessels (Moore[159]) According to O Hare and Walker[160] in hypertension, at least, the condition of these vessels must be an index of the condition of similar vessels all over the body The finding of definite sclerosis of the retinal arteries is evidence of hypertension present or past In a series of 50 cases of hypertension with peripheral arteriosclerosis studied by O Hare and Walker[160], 68 per cent showed a degree of retinal arteriosclerosis classified as at least 'marked' In contrast,

in 50 similar cases of arteriosclerosis without hypertension only one case showed a similar degree of retinal arteriosclerosis and only 18 per cent showed any Furthermore there is being accumulated a considerable amount of material which indicates that in many of the chronic myocarditis patients with muscle failure and normal or low blood pressures the finding of thickening of the retinal vessels is an indication of a previous hypertension Consequently it seems that the condition *of the retinal arteries is one of the most important and productive parts* of the examination of every cardio vascular renal patient

Wagener[337] in 1945 published an excellent review of this subject to which the reader is referred

Blood

The most important change in blood morphology in Bright s disease is a reduction in hemoglobin and a decreased red blood cell count There is little or no change in these in acute Bright s disease but in chronic forms this may become marked especially in chronic Bright s disease without edema Here counts of 2 500 000 and 2 000 000 are common and the red cell count may approach a severe grade with counts of 1 500 000 to 1 000 000 At first the hemoglobin red cell ratio is of the normochromic or hypochromic type but later the color index *sometimes increases and a hyperchromic anemia develops which may resemble* a pernicious anemia In the severer anemias some variation in size shape and *staining reaction of red cells appears and nucleated forms may be seen The* anemia in acute hemorrhagic cases is normochromic or hypochromic usually moderate in degree

The anemia of chronic Bright s disease seems definitely related to the toxic condition rather than to any loss of blood from hematuria Repeatedly I have seen patients with long continued hematuria show almost no anemia while in patients in whom hematuria was never observed anemia was very marked The reaction of the blood in chronic Bright s disease suggests a toxic effect on the blood cell forming apparatus It is a result of some factor decreasing bone marrow activity This is not true of acute Bright s disease[79]

A progressively increasing anemia is of almost the same prognostic significance as a decreasing phthalein excretion or an increasing blood nitrogen In fact repeated blood examinations may be used as a valuable index of renal function The patient with a severe anemia often has the sallow slightly yellowish appearance of one with pernicious anemia and a mere glance at the face may reveal the serious *prognosis It is of interest that this appearance is quite different* from the pale pasty pallor of some acute cases and of many cases with edema *Here the pallor results from edema of the skin or from vasoconstriction and the* hemoglobin and blood count may be essentially normal

Leucocytes as a rule show little departure from the normal *In acute Bright s*

disease there may be a slight polynuclear leucocytosis rarely a quite marked one. In the severe anemia of chronic Bright s disease there may be a leucopenia with a slight relative increase in the lymphocytes

Blood platelets show no change except in association with severe anemia, when they may be decreased in number

Parathyroids

Hyperplasia of the parathyroids is a frequent finding in autopsies on patients dead of long continued chronic Bright s disease[161–163] The parathyroids are generally enlarged rather than showing the localized hyperplasia or adenoma formation commonly seen in hyperparathyroidism unassociated with Bright's disease Sometimes when not grossly enlarged sections of the parathyroids show hyperplasia The parathyroid hyperplasia found with chronic Bright's disease is of the secondary not the water clear type, i e, the predominant cells are not of the enlarged vesicular form Albright and his associates[164] suggest that the phosphate retention in Bright's disease is the cause of the parathyroid hyperplasia and associated decrease in blood calcium In animals they have produced a similar condition by continued injections of phosphate If the Bright's disease occurs in the period of growth dwarfism and bone changes occur Renal calcinosis may develop

Bones

In some patients with chronic Bright's disease bone changes are found[165 166 170–173] There may be osteoporosis with decalcification or occasionally osteitis fibrosa cystica Such terms as renal osteodystrophy renal rickets, renal dwarfism de Toni Fanconi disease, nephrocalcinosis with rickets and dwarfism and renal nanism have been applied Dwarfism is present when the disturbance becomes well developed before the period of growth of the patient ceases[167 170]

Various explanations of the mechanism of the bone changes have been offered Some think that parathyroid hyperplasia is an important factor in cause this in turn related to phosphate retention and decreased blood calcium[164] Others think that acidosis from renal insufficiency is an effective factor Others think that much of the skeleton change and lack of growth come from the malnutrition of severe Bright's disease X ray examination of the bones will show the skeletal lesions that are characteristic of several forms of the condition it is the most important means of diagnosis

In patients showing the nephrosis syndrome x ray has shown generalized rarefaction of diaphyseal bone and relatively good calcification in the regions of

epiphyseal growth usually with normal rate of bone growth and no signs of rickets or other skeletal deformity[272] With these skeletal changes go an abnormally low serum calcium concentration a high excretion of ingested calcium in the feces and a virtual absence of calcium from the urine Presumably failure to store calcium at a normal rate leads to the skeletal decalcification demonstrable by x ray Bone matrix formation seems normal calcification of the shafts of bones is incomplete because of deficient supply of calcium but the epiphyses of growing bones are favored with regard to calcium distribution[273] Additional discussion will be found in Chapter XI-A and Chapter XIX Vol III of Oxford Medicine

Skin and Mucous Membranes

Both the body surfaces the outside and the inside ones show changes to cause some of the symptomatology of Bright s disease in particular that of chronic Bright s disease with azotemia Some authors include these changes among the features of uremia

Skin — Edema discussed elsewhere in this chapter is a frequent disturbance of the skin in both acute and chronic Bright s disease In moderate degree it is the cause of the pasty pallor of many patients a pallor suggesting anemia but due to separation and covering over of the capillary network of the skin by the excess of fluid in the skin These patients however are not anemic for at this time they have normal red blood cell counts and normal hemoglobins When edema is marked the skin takes on a shiny pallor and is dry it may split and long leak fluid through the splits With massive edema of the skin there is discomfort from the tenseness and awkwardnes even difficulty in movement of the extremities Edema of the genitalia often causes great discomfort and even makes urination very difficult When the edema recedes typical striae albicantes may appear Infection of the subcutaneous tissue and the skin is not infrequent and ulcerations may develop

In chronic Bright s disease the skin often takes on a peculiar yellowish brown tint Some believe this is caused by the retention of urochromogen ordinarily excreted in the urine which in the skin is converted by the action of light into actual pigment[199] at any rate the coloration is most marked on the exposed surfaces of the body If as often happens the patient with chronic Bright s disease becomes anemic the anemia also is a cause of yellowish or brownish yellow pigmentation of the skin The skin tends to be dry With cardiac insufficiency edema appears In patients with high degrees of urea retention the urea may be excreted in the sweat and with drying form shiny crystals

Pruritus is a common symptom very uncomfortable and very intractable in patients with advanced Bright s disease With it extensive scratch marks mar the skin surfaces and may become infected

A variety of skin eruptions is seen in patients with severe Bright's disease They take on many forms, none characteristic of the condition, they may be erythematoid eczematoid, urticarial, purpuric or lichenoid in character On histological examination a necrotizing change is seen frequently

Mucous Membranes —As with the skin, edema may involve the mucous membranes In the gastrointestinal tract edema can affect the entire wall and hinder its peristaltic activity but sometimes instead of this the escape of fluid into the stomach and intestine causes vomiting and diarrhea respectively Edema of the glottis rarely may be serious causing dyspnea, cyanosis and even suffocation Edema of the uvula, pharynx and tongue may appear and makes swallowing difficult The edema of Bright s disease may cause pulmonary edema, although usually the pulmonary edema is caused by the secondary cardiac decompensation Often the edema of the subcutaneous tissue is associated with serous effusion into pleural pericardial and peritoneal cavities

In chronic Bright's disease with azotemia glossitis, stomatitis [04], enteritis, colitis proctitis, cystitis and vaginitis may appear The lingual and buccal mucosa at first is dry and glazed Later on the tongue a thick foul usually dark brown, sometimes gray coating appears sometimes easily removed sometimes very adherent which if removed is painful and leaves an eroded surface In it spirochetes and fusiform bacilli often are present Salivation is common With this teeth may loosen and the gums swell and bleed

Loss of appetite nausea and finally severe intractable vomiting point to involvement of the gastric mucosa Inflammatory changes in the mucosa of the intestine will cause diarrhea with watery mucous bloody, foul stools Peyer s patches and solitary follicles are hyperplastic and may ulcerate Extensive diphtheritic membranes may form in the intestine bladder and vagina [00] In this exudate may be found the spirochetes and fusiform bacilli as in Vincent's angina, these appear to be secondary invaders Similar exudate sometimes forms in the larynx trachea and bronchi [09]

The pathogenesis of these various mucosal inflammatory lesions is believed by some to be primarily from the excreted urea being decomposed into ammonia [01 03] The bacteria normal to the mouth and intestine and the ammonia cause local injury even necrosis The urea itself is not injurious Possibly some other as yet unidentified toxic substance may be causative of the mucosal lesions The microorganisms which are present are considered to be secondary invaders Often in these lesions the arterioles show endarteritis and this may lead to local anemia and necrosis as causative factors in these lesions

PATHOLOGICAL PHYSIOLOGY

Renal

The kidney is the chief excretory organ of waste products of body metabolism It has a large share in excreting water sharing this function with the respiratory tract the digestive tract and the skin these together remove excess of ingested water and of that derived from the katabolism of the food supply and of tissue constituents The kidney plays a large part in maintaining the body s homeostasis The electrolyte level within the body and the acid base balance necessary to normal function is maintained within the required narrow limits in large measure by renal activity Disturbance of renal activity caused by the pathological changes in the kidneys in Bright s disease is responsible for what the physician observes in his patients with any of the various forms of Bright s disease enumerated in the section on Clinical Classification and described in the pages of Part II

The pathological lesions of the kidney in Bright s disease are complex and involve in varying degrees all of its structures as has been described in the previous section on Pathology Of these the lesions in the glomeruli take dominance[21 305] while those in the tubules are of lesser significance Function of the tubules is influenced to considerable degree by changes in the intertubular circulation changes which result from vascular disturbance in the glomeruli and their afferent and efferent arterioles whence comes the bulk of the blood to the vessels between the tubules Kidney function depends on a balanced interplay between glomeruli and tubules the former acting as a filtration membrane the latter chiefly as a mechanism of absorption but also to a lesser degree as a mechanism of excretion and of manufacture the final composition of the urine being the result of the coordination of these several activities Swelling of the kidney against the resistance of a stretched capsule by increasing intrarenal pressure can influence renal circulation and glomerulotubular function to reduce urine output even up to the point of anuria Any pathological change that increases renal bulk is capable of increasing intrarenal pressure uch changes are dilatation of glomeruli and tubules swelling of cells lining tubules edema cellular exudation and/or hemorrhage into the interstitial tissue and infiltration of kidney with neoplastic cells If the kidney capsule has undergone any prior fibrosis it will be less capable of stretching against intrarenal pressure and this will increase the effect of any of the changes mentioned in the last sentence

Lesions of the glomerulus may decrease filtration activity leading to retention they may cause leakage into the tubule of substances not normally passing through the glomerular structures or they may cause a combination of retention and leakage Intraglomerular lesions and lesions of the afferent and efferent arterioles may decrease blood flow through the glomerulus and thus influence glomerular

filtration All of these changes affect also function of the tubules, which is influenced further by degenerative changes in the cells lining the tubules

A very slight lesion of the walls of the glomerular capillaries and their covering layer even one so slight as not to be visible under the microscope unless special staining methods are used, and sometimes not even then, will allow the passage of molecules larger than those normally passing into the tubules such as those of albumin and globulin and so albuminuria becomes one of the earliest evidences of Bright's disease and, since this leakage persists although often as time goes on in decreasing amounts, albuminuria continues throughout the course of Bright's disease Formerly it was thought that albuminuria originated solely from glomerular leakage but recent observations indicate that the tubules also play a part in its mechanism as has been discussed already in a previous section of this chapter

A somewhat more marked lesion of the wall of the glomerular capillary and its covering layer will permit the leakage of bodies larger than molecules of protein such as red blood cells and thus glomerular lesions of certain types are an important source of hematuria Hematuria also results from lesions of the intertubular blood vessels with escape of red blood cells into the interstitial tissue and thence through the basement membrane of the tubule to pass between the lining cells into the lumen of the tubule and enter the urine Hematuria, slight or great is a very constant feature of acute Bright's disease and occurs also in the exacerbations of chronic Bright's disease From what already has been said it is evident that hematuria will be accompanied by a varying degree of albuminuria, while albuminuria often will not be accompanied by hematuria In Bright's disease hematuria may be massive accompanied by slight albuminuria or albuminuria may be massive with no or slight to marked hematuria depending on the nature and severity of the renal lesion

The lesions in the kidneys already described and discussed have a two way influence they cause to be retained in the body products of body metabolism normally excreted from the body by way of the kidneys and they cause to be lost from the body certain substances which normally remain in the body These two processes usually are in action at the same time but not necessarily in proportionate degree Also the degree of activity of each process varies from patient to patient at a given time as well as from time to time Also variations in rate of both retention in, and loss from the body of different substances occur Furthermore, retention or loss of any one constituent may cause disturbances in the balance of other substances in the body with increase or decrease in their amount These changes are mirrored in the composition of the blood plasma and concern those substances already discussed in the section on Blood Chemistry The chief function of the kidney in body economy is to maintain an equilibrium within the body of the constituents of blood and body fluids compatible with normal functioning of body organs and tissues while removing from the body substances which might prove deleterious Variations within only narrow limits can take place in these without seriously disturbing body function Consequently very slight shifts may have serious con

sequences The effects of these changes cause the significant symptoms of Bright s disease Water balance in relation to edema and dehydration acid base balance in relation to acidosis and alkalosis and toxic retentions in relation to uremia confront us for discussion as important items in the pathological physiology of Bright s disease

Edema

Edema is a very frequent occurrence in Bright s disease The clinical features of it will be discussed in Part II Clinical Aspects of Bright s Disease The mechanism *of edema is complex and usually several factors combine in the causation* of the edema of an individual patient whatever the determinant causative pathological condition present Yet certain causative factors preponderate in any one of the various forms or types of edema and on the basis of its pathological physiology distinguish them Thus *the chief mechanisms of edema of inflammatory*

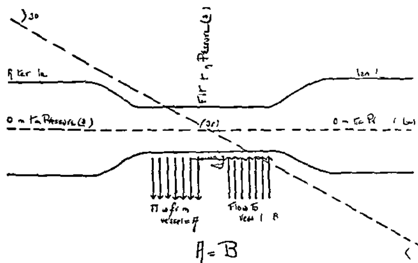


FIG 23 — Diagram showing relation of fluid flow to and from connective tissue spaces surrounding small blood vessel when filtration pressure and osmotic pressure are equal in mid portion of the capillary no edema is present (from Christian[177])

lesions of cardiac decompensation of lymph stasis of acute Bright s disease of chronic Bright's *disease of starvation (hunger) of vitamin deficiency and of* urticaria and serum sickness are not the same[186]

In all edema there is a disturbance variously brought about in the balance of flow of fluid from the arterioles and capillaries into the tissues and its return flow from the tissues back into the venules and lymphatics (see Figs 23–25)[177] Such flows are a normal almost continuous process and so long as outflow from tissues is equal or greater than inflow edema does not develop Conversely edema

does develop when more fluid is poured into the tissues than is being drained out of them back into the vascular and lymphatic circulation Such descriptive terms as circulatory edema cardiac edema renal edema, nephritic edema, nephrotic edema inflammatory edema, etc are in use expressing causative relationships The disturbances most important directly or indirectly in the mechanism of edema, as it occurs in Bright s disease are increase in hydrostatic pressure within the vascular system, variation in colloid and electrolyte osmotic or oncontic pressure in the plasma and tissue fluids and injury to the walls of arterioles, capillaries and venules with some effect from changes in acid base balance

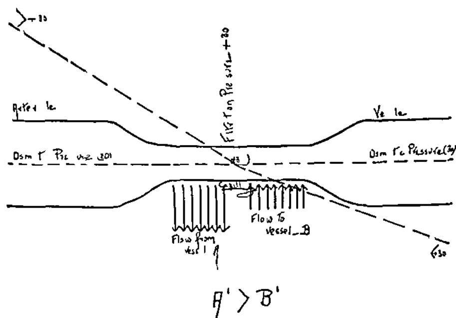


FIG 24 — Diagram showing relation of fluid flow to and from connective tissue spaces surrounding small blood vessel when filtration pressure has increased over osmotic pressure in midportion of the capillary edema is present (from Christian[17])

Edema fluid contains the same substances as are found in blood plasma but the percentage of each differs conspicuously Water is the largest component of each Edema fluid contains much less protein more chloride and less potassium than found in blood plasma while sodium calcium bicarbonate, phosphate urea, glucose and non protein nitrogen exist in approximately the same concentrations in each These differences particularly the difference in protein content, are important in the osmotic pressure balance of the two fluids Both blood plasma and edema fluid have the same freezing point indicating an identical molecular concentration Protein content of edema fluid usually very low as compared with

that in plasma varies in amount in different varieties of edema Fluid accumulating in the serous cavities of the edematous patient in composition is much like that of the fluid in the tissues except that its protein content usually is higher

The vessel wall separating the blood stream from the tissues behaves physiologically as a semipermeable membrane through which water and substances with small molecules such as the crystalloids pass freely while substances with

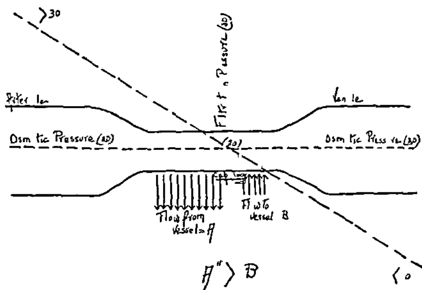


Fig 25 —Diagram showing relation to fluid flow to and from connective tissue spaces surrounding small blood vessel when osmotic pressure has decreased below filtration pressure in midportion of the capillary edema is present (from Christian[1])

large molecules such as albumins and globulins do not pass or pass only in exceedingly small amount under conditions of normality Some observations have suggested *that with marked dilatation of the blood vessels with stasis some colloids* of large molecular size do pass through normal capillary walls others believe that in experiments suggestive of this actual injury has been done to the capillary wall, and injury as under other conditions has brought about abnormal capillary permeability

Regarding the vessel wall as a semipermeable membrane we need to consider as factors leading to edema the effect of variations in hydrostatic pressure within the *arterioles capillaries and venules in opposition to the colloid osmotic pressure* of their contents as diagrammatically shown in Figs 23–25 and the action of Donnan s law in relation to the electrolyte composition on the two *sides of the*

does develop when more fluid is poured into the tissues than is being drained out of them back into the vascular and lymphatic circulation Such descriptive terms as circulatory edema, cardiac edema renal edema, nephritic edema, nephrotic edema inflammatory edema, etc are in use expressing causative relationships The disturbances most important directly or indirectly in the mechanism of edema as it occurs in Bright s disease, are increase in hydrostatic pressure within the vascular system, variation in colloid and electrolyte osmotic or oncontic pressure in the plasma and tissue fluids and injury to the walls of arterioles, capillaries and venules with some effect from changes in acid base balance

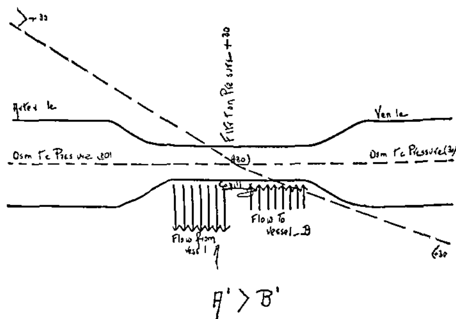


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Under normal conditions in man Landis has found that hydrostatic pressure in the arteriolar limb of the nail bed capillary averages 32 mm of mercury in the end of the loop 20 mm and in the venous limb 12 mm The colloid osmotic pressure of man s blood plasma according to Starling[1] , Govaerts[1] Fahr[1] and others averages about 25 mm of mercury According to Van Slyke quoted by Fishberg on p 130 of his book, of this the protein molecules cause an actual osmotic pressure of about 20 mm of mercury, while about 5 mm depends on the Donnan equilibrium in the distribution of diffusible ions

Another factor in osmotic pressure may lie in the high content of the blood plasma of some patients with chronic Bright s disease in fatty acids lecithin and cholesterol, which, according to E H Fishberg[1 8], exert some osmotic pressure and so in part compensate for the decrease in plasma protein Others do not agree with this view Dilution and dissociation of proteins with changing hydrogen ion concentration are additional factors of influence on colloid osmotic pressure

The parts played by sodium chloride and by hydremia in the mechanism of edema now are recognized as secondary an increase in intake of sodium chloride and of water if not very excessive will not cause edema under conditions otherwise normal but both will increase an edema caused by any of the factors so far enumerated Consequently reduction in the intake of sodium chloride and water are important in the therapeutic management of patients with edema as is seen repeatedly in the clinic[189 19 196] and can be demonstrated in various animal experiments[193–19] that produce an edema analogous to that observed in patients With regard to sodium chloride it is the sodium that is most important[18 190] since it can be shown that other chlorides may be retained in the body without increasing edema and some such as ammonium or calcium chloride, actually have a diuretic effect

That sodium chloride is not a primary but a secondary cause of edema is shown by the patient with a Bright s disease causing marked renal insufficiency in whom plasma sodium and chloride are much increased but no edema appears unless cardiocirculatory failure is superimposed this has been called dry salt retention Similarly with mechanical obstruction of the urinary passages causing anuria there may be seen an enormous increase in plasma sodium chloride without any edema appearing In the same cases even a large intake of water fails to cause edema apparently the other routes of excretion of water from the body being sufficient to prevent its accumulation in the body even when no renal excretion is taking place However Ivy and his associates [97] found that in dog after bilateral nephrectomy excessive intake of both water and sodium chloride would cause massive edema while nephrectomy alone and excessive water intake alone failed to cause edema In chronic renal insufficiency in man the specific

semipermeable membrane formed by the thin vascular wall as well as possible damage to vessel walls increasing their permeability to substances of considerable molecular size It has been possible to determine directly in man by means of a hard glass capillary tube introduced into capillary loops of the skin at the base of the finger nail the intravascular hydrostatic pressure[1, 8, 183, 184] and to measure by means of an osmometer the osmotic pressure of the plasma[1, 9, 180, 181, 308] These measurements show that under normal conditions these two factors hydrostatic and osmotic pressure, balance each other in such a way as to cause an outflow at one end of the capillary system and an inflow at the other, and that edema results when this balance is upset by either rise in hydrostatic pressure or fall in osmotic pressure Furthermore edema will develop, if from any cause capillary permeability is increased, so as to allow of the passage into the tissues of substances with large molecules such as protein along with water and crystalloids Edema too can be brought about by an increase of crystalloids in tissue fluid in relation to their content in blood plasma As already indicated, while change in one of the factors just enumerated preponderates in any particular type of edema some change occurs also in other factors, and edema of all kinds is a complex mechanism not running directly parallel to change in a single factor

It is important to remember that colloid osmotic pressure is related to size of the molecule and so varies in relation to the composition of plasma protein and only indirectly in relation to its amount Since such values for molecular weight are given[18, 308] as for plasma albumin 45 000 69 000 according to others[308] pseudoglobulin 81 000 euglobulin 135,000 and fibrinogen even larger, and since the smaller molecules exert the higher osmotic pressure it is obvious that a decrease in plasma albumin is much more effective in lowering osmotic pressure than a decrease in plasma globulin The difference in the osmotic pressures of these several proteins is very considerable as shown by Govaerts[179] estimate that 1 gram per cent of albumin exerts a colloid osmotic pressure of 7 54 cm of water while 1 gram of globulin exerts a pressure of only 1 95 cm of water

As the protein with the smaller molecular weight passes the injured glomerular membrane more easily than the one with the larger in Bright s disease with edema the decrease when it occurs is proportionately greater in the albumin fraction of the total plasma protein than in the globulin and fibrinogen fraction, hence we speak of a shift in the albumin globulin ratio as an important finding in relation to the appearance of edema It is important for clinical purposes to quantitate separately plasma albumin and plasma globulin if facts significant in an understanding of the mechanism of edema are to be obtained Unfortunately the technical methods for these determinations are difficult to carry out with great accuracy and so reports on them are liable to variations apart from the exact composition of plasma protein in albumin and globulin

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as a rule comes somewhat later in the course of the disease than the form of edema discussed in the previous section Usually it develops in patients into whose urine much protein has been escaping from the blood plasma by reason of continued marked albuminuria This has caused a reduction in the protein content of the blood plasma affecting the albumin more than the globulin as can be determined by chemical analysis or electrophoresis and causing a fall in colloid osmotic pressure of the plasma Direct measurement of the osmotic pressure of the blood shows that this is below normal value This lowered osmotic pressure leads to a shift of water to the tissues more water passes from the arterioles and capillaries by reason of the hydrostatic pressure in them than is being reabsorbed into the capillaries venules and lymphatics under the decreased osmotic pressure of their contents and this results in the accumulation of fluid in the body tissues *and body cavities i e in generalized edema or anasarca as is illustrated in the diagrams (see Figs 23–25)* As in this form of Bright s disease the edema fluid contains only very slight amounts of protein its very slight osmotic pressure plays only a minimal part in influencing the effect of the decreased osmotic pressure of the plasma protein

It seems proved that the primary and chief cause of the edema of this form of Bright s disease lies in the decreased plasma protein and mainly the decrease in plasma albumin caused by the loss of these substances by way of the urine However since we see edema increase and decrease in patients when no demonstrable changes are taking place in the plasma proteins it is evident that others of the factors causative of edema already discussed play a part in the mechanism of this edema notably water and sodium chloride intake change in capillary permeability and variation in intravascular hydrostatic pressure from various causes

In general those patients with chronic Bright s disease in whom albuminuria is slight do not develop edema except during acute exacerbations during which the edema is like that occurring in acute Bright s disease and probably due to the development of abnormal capillary permeability or when it is caused by circulatory failure in sequence to the development of high blood pressure or of myocardial insufficiency leading to a rise in the intracapillary hydrostatic pressure The latter is the edema of the kind that occurs in cardiac decompensation without Bright s disease

In this group of cases as renal function fails anemia often develops and with this comes another possible cause of edema an edema incident to anemia an edema of complex mechanism in which both capillary permeability and decreased plasma protein play parts In patients with this form of Bright s disease excessive edema *occurs only when cardiac decompensation develops* even though renal insufficiency becomes so great as to lead to uremia

gravity of the urine is constantly low because of the difficulty of the kidney in excreting solids This leads to polyuria, which in a way is a factor in preventing edema, it is a sort of continuous diuretic effect

In addition to the factors already discussed some observations indicate that the central nervous system, notably the hypothalamus, controls water exchange and suggest that lesions in this region may cause edema[198] and be an etiological factor in certain patients regarded as having the nephrosis syndrome

After this somewhat general discussion of the mechanism of edema let us turn our attention to it in the various forms of Bright s disease

Edema usually of slight degree and distributed particularly about the eyes, is an early and frequent manifestation of acute Bright s disease edema greater in amount and more extensive in distribution sometimes occurs in acute Bright s disease The mechanism of this type of edema still is under discussion Probably the former type is caused by increased permeability of the capillaries very probably some toxic substance has injured the capillary wall to cause this change possibly water retention accompanying the oliguria of acute Bright s disease is an additional causative factor

This is a view very generally held but the toxic substance has not been demonstrated directly up to now and measurements of blood volume show no constant increase its variations in acute Bright s disease being no greater than observed in other patients lacking edema At this early stage in acute Bright s disease, when edema first appears the colloid osmotic or oncontic pressure of the blood plasma and the electrolyte content of plasma and tissue fluids seem not sufficiently changed from normal to explain the edema In the more marked type of edema, although plasma protein level may be but little lowered there is a considerable reduction in the plasma albumin and a consequent decrease in colloid osmotic pressure this is important among the causative factors of the edema as discussed in the next paragraph

The very early appearance and the distribution of the lesser degree of edema does seem to fit best to a local capillary injury such as would result from the presence of something injuring the wall of the capillary and increasing its permeability This could be of the nature of an allergic reaction just as is the explanation of many observers for the development of the glomerular lesions of acute Bright s disease It is to be remembered that local edema is an early reaction of tissues in inflammation that acute Bright s disease develops very often in sequence to streptococcal or other coccal infections particularly those of the throat, and that with the infection there is a reasonable basis for assuming either a circulating toxin or a circulating allergen to injure capillary wall or bring an allergic response to a sensitized tissue

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Dehydration

Dehydration is a much more important factor in Bright's disease than has been recognized generally in the past It occurs often in those varieties of chronic Bright s disease in which azotemia is developing It even may complicate the picture in the presence of edema, particularly the edema of coincidental or secondary cardiac insufficiency It may result from the chronic polyuria of the patient with a urine of low, fixed specific gravity It may follow a marked diuresis of any cause The frequent vomiting and sometime diarrhea of advanced chronic Bright s disease are potent causes With the water loss there is a decrease in plasma concentration of sodium and chloride Its correction may relieve very annoying symptoms and improve strikingly the patient s condition It is to be recognized from such clinical appearances as dry skin, dry, shrunken, often red tongue decrease in saliva causing uncomfortably dry mouth, which decreases appetite and makes eating more difficult and unpleasant, shrunken cheeks, sunken eyes, softened eye balls and decreasing urine output Sometimes some of these symptoms are considered to be caused by the azotemia To give the dehydrated patient water and sodium chloride, preferably intravenously, in the form of 5 per cent glucose solution in 0 85 per cent sodium chloride solution not only will relieve the dehydration but often will improve renal function and ameliorate, temporarily at least, sometimes for a considerable period, many of the patient's symptoms[199]

Acid base Equilibrium Acidosis Alkalosis

The maintenance in the body of acid base equilibrium or acid base balance to keep the pH level of blood plasma and body fluids and tissues within those narrow limits essential to their function and to life depends on the excretion from the body of any substances whose excess would disturb this equilibrium in the direction of acidity or alkalinity i e would decrease or increase their pH To this end the ability of the normal kidney to neutralize and excrete excess acid derived from the food and from the katabolic processes going on within the body is very important the kidney from an alkaline glomerular filtrate forms an acid urine but with an excess of intake of alkalies and under some other condition the usual acid urine becomes neutral or alkaline

Acidosis —In severe Bright s disease especially with uremia and its accompanying vomiting and dehydration normal acid base balance is disturbed, and acidosis results[200] alkali reserve of the body is reduced in the neutralization of acid in order to maintain as far as is possible plasma and body fluid pH within its normal values Acidosis involves a depletion of the bicarbonate in the blood, which has been termed the first line of defence ' against acidosis Protection

against acidosis is brought about by elimination of carbon dioxide by the lungs in which sodium bicarbonate plays a large part as a carrier by the neutralization of acid by the ammonia formed by the kidney by phosphate[201] and sulfate retention and by elimination of acid by the kidneys Retention of organic acids except that incident to a coincidental starvation seems to play a rather minor role *in the acidosis of Bright s disease Renal disease influences adversely these functions and so when marked* causes acidosis which except in far advanced lesions remains moderate in degree not comparable to the severity of the condition that so readily develops in diabetes mellitus In estimating the presence and severity of acidosis in the patient with Bright s disease the determination of the serum chloride level and the serum carbon dioxide combing power gives us a fairly accurate indication under most circumstances and permits us to decide whether sodium chloride or sodium bicarbonate or both should be administered *or withheld Estimation of blood urea nitrogen or non protein nitrogen and of* plasma protein serve us as further guides in treatment

Alkalosis —Alkalosis is infrequent in Bright s disease unless brought about by an excess intake of sodium bicarbonate and calcium carbonate as may occur in the treatment of peptic ulcer of the stomach or duodenum Under these conditions a decreased kidney function increases the probability of the development of alkalosis and its occurrence should direct attention to a possible unrecognized *Bright s disease* Alkalosis *so caused very markedly disturbs renal function* and leads *to nitrogen retention and hypochloremia When carbonate ingestion* is stopped changes in blood chemistry return more or less quickly to normal although evidences of impaired renal function may persist for several weeks Sometimes the severe vomiting of Bright s disease may produce an actual alkalosis

Uremia

Uremia is *a term* used at *present* for the clinical condition which appears in patients with severe often advanced Bright s disease So far there is practical agreement but beyond this there is much difference of opinion as to what clinical disturbances should be included under uremia and as to how they are caused in relation to the severe disturbance in renal function which exists The term uremia was introduced by Piory [02] about 1840 to designate an intoxication from *the inability of the kidney to purify the* blood *literally the word means urine in* the blood Some would so limit the use of the term implying that all the changes to be included under uremia are toxic in nature caused by substances which are in the blood because the kidney fails to eliminate them Others include in uremia disturbances caused by lesions in the central nervous system broadly related to disturbed circulation incident or secondary to changes resulting from

the renal lesions of Bright's disease while others would separate these from uremia under such terms as extrarenal or false uremia, pseudouremia, hypertensive encephalopathy, eclamptic uremia etc

Foster [93] defined uremia as follows by uremia we understand an intoxication manifested by psychomotor disorders which is apt to supervene in nephritis My own definition in an earlier (1920) edition of this chapter [94] defined uremia as the toxic manifestations of renal insufficiency, in particular those that arise from disturbances of the central nervous system Twenty four years (1944) later I have said of it [95] ' A symptom complex due to toxemia from renal insufficiency, uremia is difficult to delimit clinically, separating the symptoms that result from toxemia from those due to edema vascular disturbances, etc, which often occur with, but are not caused by renal insufficiency Occur ing most often in Bright's disease it does appear in other conditions usually from great restriction in renal blood flow, which in turn causes a great decrease in renal function Among such conditions are shock great dehydration as from severe vomiting and continued watery diarrhea notably in cholera the hepatorenal syndrome, diabetic coma, crises in Addison's disease after profuse hemorrhage particularly hematemesis the circulatory collapse of acute infectious diseases etc"

Garrod [96] included a variety of functional disturbances of supposedly toxic origin as well as such definite anatomical changes as the gastrointestinal ulceration stomatitis and pericarditis encountered for the most part in the late stages of Bright's disease Ascoli went even further and considered as uremic almost any of the symptoms of Bright's disease Atchley (1943) writes [97] "Uremia may be defined as a clinical pattern associated with renal insufficiency and nitrogen retention The uremic state manifests itself in many ways, but for the purpose of exposition one may indicate two major types of effects on the organism In one group are found the relatively well understood physiologic complications of advanced renal insufficiency acidosis dehydration and disordered calcium metabolism On the other hand there are a large number of symptoms and signs that are apparently toxic in origin, although the nature of these poisons has defied analysis In this latter group are found such phenomena as headache, vomiting itching of the skin pericarditis and anemia" He includes also in his discussion of 'toxic manifestations disturbances in the mental state restlessness insomnia and coma muscular twitchings and convulsions, stomatitis diarrhea with ulcerative colitis, membranous lesions of larynx and trachea Atchley[207] also uses the terms extrarenal uremia and pseudouremia, including under the latter cerebral disturbances incident to edema hypertension and alterations in the circulation due to vascular spasm or actual damage

Fishberg[98] in his book writes "We may define uremia, in accord with its etymology and original meaning as the symptom complex resulting from renal

insufficiency and accompanying the retention of urinary constituents in the organism No group of symptoms is to be considered as uremic in nature unless it occurs in the presence of abnormally high non protein nitrogen in the blood Symptoms referable to the central nervous system not associated with abnormally high non protein nitrogen in the blood are explained by the use of the term hypertensive encephalopathy suggested by Oppenheimer and Fishberg[151] Volhard[108] expressing his ideas somewhat similarly uses the terms true and false or extrarenal uremia under the latter false or extrarenal uremia he classifies *a variety of symptoms originating chiefly from the central nervous system that* occur even when renal insufficiency is not present Here he goes on to say we are forced to recognize two separate groups the first acute eclamptic uremia is frequently encountered in acute and subchronic diffuse nephritis and still more frequently in eclampsia of pregnancy but rarely in nephrosis the second *consisting of the pseudouremic circulatory phenomena occur in chronic primary* or secondary hypertension

Harrison and Mason[99] in their discussion of the pathogenesis of the uremic syndrome express very similar views saying the term uremia as employed in this review designates only that symptom complex which occurs in conjunction with and as the result of *the retention in the blood of urinary waste products* and does not refer to the clinical syndromes of pseudouremia and of hypertensive encephalopathy which although of frequent appearance in nephritic patients have been clearly demonstrated to be independent of renal insufficiency

Another view of the problem of the cause of uremia stresses disturbances in *metabolic balance brought about by renal insufficiency emphasizing that the most* important function of the kidney is to maintain within quite narrow limits the amounts of the many constituents electrolyte and non electrolyte present in body fluid extra and intra cellular The latter is a view of renal activity well expressed by A M MacCallum[8] in 1918 and quoted in the several paragraphs *ending the section on Normal Renal Structure and Function in an early part of* this chapter Recently 1946 a reviewer[45] has expressed it as follows According to modern theory the components of the body are in a state of continual change Thus the constancy of any biologic structure does not imply stability but denotes a balance of the processes of degradation and regeneration in which *its ingredients participate Complex molecules of all types break down or lose molecular groups and are again rebuilt or regain lost groups* This intricate and cyclic activity takes place in a circulating so called metabolic pool in which small molecules derived from degradation or digested food are carried throughout the body Likewise the mineral constituents of cells and body *fluids are in dynamic equilibrium unhergoing continuous movement* and exchange

It is obvious that the position of the kidney in this activity is extremely important since it governs the composition of the metabolic pool through its regu

lation of the chemical structure of the plasma, although the factors involved are obscure It is equally probable that the kidney acts to maintain the constancy of some single plasma characteristic, such as ionic strength, osmotic pressure water, base or hormone content or the constancy of several In any case, the net result is a remarkably small range of variation in the composition of the plasma under diverse conditions Since the plasma is in equilibrium with the remainder of extracellular fluid, which in turn, is in equilibrium with intracellular fluid in most respects it follows that renal activity determines the structure of all body fluids making up the metabolic pool

Although many biologic processes are, to a large extent, independent of the composition of the metabolic pool it seems certain that extensive changes, such as those occurring during renal insufficiency, may disturb chemical reactions everywhere in the body and ultimately lead to fatal dislocation of the metabolic balance According to this view, it is gratuitous to seek an explanation for the clinical manifestations of uremia in the renal retention of specific toxic waste products Any great loss of water and electrolytes with a retention of catabolites by the damaged kidneys, is sufficient to provoke serious disturbances of cellular activity, with resultant clinical phenomena Thus a study of the chemical structure of the blood during renal disease reveals not only the effects of renal dysfunction on body fluids, but also the causes of cellular dysfunction elsewhere in the body"

The view just quoted along with those of Harrison and Mason [09] already referred to, probably expresses as well as is possible at this time a satisfactory concept of the mechanism or pathogenesis of the condition known as uremia

After reading the several in extenso definitions just quoted one has obtained an excellent epitome of the present day views about uremia There is general agreement that in Bright s disease, when it greatly restricts renal function certain symptoms as enumerated in various of the preceding definitions, appear which are related in a causative sense to what the kidney is not accomplishing in its activity as compared with its work under conditions of normal structure and function The earlier views, which referred all of these changes to the effects of a single toxic substance retained or formed in the body as a result of renal insufficiency have been changed now to the opinion that part of them have such a toxic cause, not a single substance as the cause but the cause in the toxic effects of a considerable number of retained substances, and that part of them have a structural cause in disturbances in the central nervous system, largely organic and related in the main to disturbances in the cerebral circulation To this there is general agreement Differences of opinion, however remain as to which of the nervous system manifestations are in the group of toxic causes and which in the group of circulatory disturbances Just what the toxic substances are still is far from agreed to

According to Foster[210] there is a grouping of symptoms of uremia to form fairly

definite types of disturbances (1) the convulsive or epileptiform type often with headache and sudden amaurosis as precursors and coma as a sequel (2) a type marked by gradually deepening coma unaccompanied by psychic disorder or signs of motor irritation (3) a type with psychic disorders commonly hallucinations and paranoid delusions often accompanied by gastrointestinal symptoms and visual disturbances from demonstrable lesions in the eye grounds Others go farther and speak of convulsive delirious comatose dyspneic gastrointestinal cutaneous pruritic and other varieties of uremia

Herrick's [11] description of a uremic attack is excellent When a convulsion occurs, there is seldom any aura as in epilepsy nor is there the cry so often heard in that disease The eyes roll upward and usually to one side the pupils dilate and for a moment the patient seems gazing with a fixed stare into distance Then a jerking of the angles of the mouth is seen the head draws to one side, the muscles of the face and neck become clonically convulsed the fingers and arms are flexed and likewise convulsed and soon the entire musculature of the body is in irregular, jerky violent motion The face becomes livid or purple foamy saliva issues from the mouth and it may be streaked with blood that comes from a bitten tongue The pulse grows rapid and weak perhaps irregular During the seizures there may be involuntary evacuation of urine and feces A few seconds or minutes are consumed by the attack which ends with a quieting of the muscular spasm a deep-drawn inspiration and a rather prompt recovery of consciousness If, however the patient has been in a stupor or coma preceding the convulsion or if the attacks are frequently repeated sleep stupor or deep coma will follow Usually the patient is somewhat dazed for a time and knows little more of the attack than that something has happened When attacks are repeated at short intervals the temperature often rises and preagonal temperaures of 105° F or over are not unusual The pulse after frequently repeated convulsions becomes rapid and weak Following an attack the patient may remain dazed for some time or may quickly return to a normal cerebral condition

All of these symptoms it would seem to the author can be considered to be toxic effects to be grouped as the direct result of renal insufficiency according to many this is true uremia To this clinical picture certainly in many patients cerebral edema acidosis and dehydration all indirect results of renal disease contribute The relief of some symptoms following lumbar puncture even though the relief is transient indicates cerebral edema as a partial causative factor Appropriate alkali therapy sometimes will cause a marked temporary change in symptoms suggesting a role from acidosis Similar effects from correction of dehydration point to it as another factor in causing symptoms in the uremic patient

Since high blood pressure and vascular disease are very frequent accompani

ments of Bright's disease, particularly of the chronic stages various symptoms will result from these, particularly symptoms associated with diffuse or focal lesions of the central nervous system and of the eye as already discussed in the section on Pathology These will receive additional consideration in the next following section on Clinical Aspects of Bright's disease Their consideration is not properly a part of the discussion here of uremia where consideration is being given to its Pathological Physiology as a toxic phenomenon

In the advanced degrees of Bright's disease, in which the symptoms of uremia as already noted occur renal function is greatly depressed, and various substances normally excreted by the kidneys are retained in the body except in so far as they seek other channels of exit Excretion by other channels such as the gastrointestinal tract, the skin and the lungs does occur and in increasing amount during decreased renal function and this serves to retard the appearance of, and to modify uremic manifestations such extrarenal excretion, however, also can and does cause additional disturbing symptoms, which play a part in the clinical picture of uremia Besides retention disturbed renal function can bring about depletion of certain substances and this may be productive of symptoms Finally in advanced Bright's disease the normal progress of metabolism of body constituents toward innocuous end products is disturbed, and intermediary products of metabolism which are toxic, may accumulate in the body and cause toxic manifestations Even substances not occurring in the body under normal conditions may be formed and cause toxic manifestations[49, 69] Obviously the mechanism of the symptoms of uremia are complex and no longer as in days past does anyone claim the presence of a single toxic substance as the cause of uremia

Much study has been made of numerous substances present in the body the circulating blood and the urine in relation to their possible role in the production of disturbances included in the symptom complex of uremia A brief review of this work now will be given to show what part individual substances can have in the pathological physiology of the toxic manifestations of Bright's disease, which are grouped under the concept uremia

Already the pathological physiology of edema dehydration acidosis and alkalosis has been discussed They play a part in the causation of symptoms of uremia sometimes directly sometimes indirectly Their discussion will not be repeated here

Chlorides — Besides retention of non protein nitrogen substances, other constituents of the blood are retained when renal function is decreased and these are potential causes of symptoms Sodium chloride is one that in the past has aroused much interest and hyperchloremia is a term once in frequent use as explaining at least some of the uremic manifestations In anuria blood chlorides may reach high values especially if no vomiting occurs Values such as 1,100

mgm [4] and 1,500 mgm [85] as sodium chloride per 100 c c of blood have been reported as contrasted with a high normal average below 620 mgm Very moderate increases in blood chloride occur in Bright s disease with the nephrotic syndrome Usually however in advanced Bright s disease a decrease occurs a hypochloremia which is very constant in patients with severe vomiting or diarrhea To chloride deficiency somnolence weakness coma hypotension hypothermia and increase in non protein nitrogen in the blood have been ascribed (Porges [1] Blum [13] Meyer [14] and their associates) Glass [1] has produced in dogs marked hypochloremia by chloride deprivation and repeated administration of apomorphine, histamine and salyrgan these dogs exhibited weakness stupor and finally coma with high blood non protein nitrogen the latter presumably from excess destruction of body protein Obviously with hypochloremia so produced there is concomitant dehydration and azotemia and so symptoms that result have a complex cause in which hypochloremia presumably plays some causative role

Potassium —Serum concentration of potassium can be increased by severe renal insufficiency [18, 1, 19] and its retention may be very toxic [9] In uremia in man associated with a high concentration of serum potassium Keith and his associates [9] saw the development of defects of intraventricular conduction in electrocardiograms This occurred both with and without the appearance of acute pericarditis or microscopic lesion of the myocardium They believe that cardiac death can be due to such potassium toxemia Fortunately in man various factors act to retard increase in serum potassium [16] In dogs intracisternal injection of potassium chloride will cause stertorous breathing twitching and rise in blood pressure but the amount necessary seems beyond levels found in spinal fluid of man in uremia [1] Potassium depletion has been observed in severe Bright s disease as a cause of great muscle weakness [7] this seems an infrequent happening

Calcium and Phosphorus —Calcium deficit occurs in the blood in renal insufficiency usually with or as the result of phosphate accumulation It has been suggested that *oxalate* retention too may be a causative factor in calcium deficit in these patients[222] and possibly *citrate* plays a similar role Calcium deficit causes increased neuromuscular irritability as is familiar in tetany In uremia twitching and muscle spasm may be related in part to calcium deficit[223] In animals such irritative phenomena follow intravenous injections of organic phosphate [224, 225] In chronic nephritis parathyroid hyperplasia may develop in relation to calcium deficiency [161, 16]

Magnesium retention has been observed in patients with marked renal insufficiency[226, 227] but it is doubtful whether it ever reaches a level to be a causative factor in patients nervous depression drowsiness and coma[228]

Urea —Symptoms like some of those in uremia can be caused by ingestion

of large amounts of urea, particularly if water intake is small Hewlett and his associates [9] produced in themselves in this way headache, somnolence, vertigo and nausea, when blood urea values rose to levels of 240 mgm per 100 c c In animals death can be caused by injecting urea, but very large amounts are required, 1 per cent of a dog's weight according to Leiter [30] Leiter obtained in these acute experiments blood levels of urea averaging 1,383 mgm per 100 c c Slow intravenous injections, using the Woodyatt pump, according to Streicher [1] cause toxicity with much less urea Obviously urea is toxic only when large amounts are used with blood levels in excess of those ordinarily encountered in Bright's disease urea retention by itself no longer can be held solely responsible for the uremia of Bright's disease, although undoubtedly it contributes an element of toxicity, although in all probability only a very minor one except in those patients in whom very marked oliguria up to anuria develops and persists It is a striking fact that often the symptoms of uremia are marked, when urea retention is only moderate Also one sees not infrequently patients without any uremic manifestations with levels of blood urea above those encountered in uremics

Other Non protein Nitrogen Substances —What can be said about retention of non protein nitrogenous bodies other than urea in relation to uremia? It is believed generally now that uric acid amino acids, polypetides and creatinin are not toxic in the range of retention which they develop in Bright's disease, although their increase may serve as an index of renal insufficiency of value in prognosis When these various non protein nitrogens are quantitated individually in the blood and total blood non protein also is determined, the figure for the sum of the former is less by a varying amount than that for the total non protein This non determined non protein nitrogen has been called *residual* or *rest nitrogen*, and some observers believe that herein lies the main toxic factor in uremia It is true that its amount increases with increasing renal retention, and it often is in very considerable amount in Bright's disease with uremia Some believe that in it are contained substances not formed in normal nitrogenous metabolism and that these bodies are particularly the toxic ones concerned in the mechanism of uremia Efforts, however to isolate in pure form such toxic bodies usually have failed although Foster[19] at one time thought he had succeeded in isolating such a toxic body from the blood of patients with Bright's disease with uremia in crystalline form as a salt of platinum and gold From a practical point of view the clinical value of determining total blood non protein nitrogen in the study of Bright's disease is about the same as for determinations of blood urea nitrogen either determination is of value sometimes in making the diagnosis more often in determining the prognosis in Bright's disease Either determination is of value when its increase is evidence of the presence of azotemia often this is of importance in separating the "toxic" manifestations of uremia from those due to sec

ondary or complicating lesions of the central nervous system of vascular origin often spoken of as hypertensive encephalopathy or as pseudouremia

Phenol — Besides the non protein group two other organic metabolites phenol and guanidine are to be considered as possible toxic factors under conditions of renal retention Retention of phenols have been held responsible for the depressed condition of uremic patients The free phenols include phenol *paracresol indole and other related substances formed in the body by deamination decarboxylation and oxidation of the aromatic amino acids tyrosine phenyl alanine and tryptophane* This change is largely by bacterial action in the intestine whence they are absorbed and detoxified by conjugation with sulfuric or glycuronic acid If this is not effective free phenols remain to exert a toxic action That this is significant in uremia is evidenced according to Beecher [32] by the following observations (1) In chronic Bright s disease blood phenols increase and this tends to parallel the severity of uremic manifestations (2) In acute nephritis there may be marked nitrogen retention without uremic symptoms and in such patients blood phenol concentrations usually are within normal levels (3) Chronic experimental phenol intoxication causes a symptom complex resembling uremia in many respects (4) Introducing aromatic amino acids into the rectum of persons with uremia increases the severity of their symptoms (5) The onset of uremic coma coincides with the appearance in the cerebrospinal fluid of free phenols Mason and his associates found in animals that twitchings rigidity convulsive movements stertorous breathing and increase in blood pressure ordinarily initiated by the intracisternal administration of inorganic *phosphate could be prevented by the previous administration intravenously or* intracisternally of free phenols The phosphate would have caused a calcium deficit and this evidence of cerebral irritation was prevented by the phenol This could explain the absence in certain uremics of irritative phenomena in spite of a calcium deficit

Guanidine retention appears to cause muscular twitching respiratory stimulation copious vomiting and frequently diarrhea [33] [34]

Is uremia solely the result of renal retention? What happens when normal kidney function ceases completely and there is no renal excretion of substances which normally appear in the urine? What symptoms result from this? In man the least complicated examples of cessation of renal function are those caused by the surgical removal of a single essentially normal kidney or the accidental ligation of its ureter these things actually have happened In animals it is easy to study the effects of removal of both kidneys an entirely analogous situation to that just mentioned as happening in man Under these circumstances the resultant changes are those caused by simple retention of what ordinarily is excreted by the kidney toxic symptoms do appear when this happens Somewhat more

complex is the situation when the anuria has been caused by obstructing calculus or neoplasm for here gradually increasing back pressure has caused pathological changes in the kidney prior to the obstruction becoming complete, and these changes may have introduced factors more analogous to the retention phenomena in advanced Bright's disease in both of these there is the possibility of retention of substances not normal to the body

When function of the normal kidney ceases completely, several days may pass before any symptoms appear If such anuria continues, life lasts a varying time in 36 cases of anuria in 11 life continued for from 4 to 7 days, in 18 from 7 to 14 days and in 7 for more than 14 days[94] Weakness vertigo, nausea dulness and drowsiness passing into coma are the usual features Headache is less frequent than the preceding Muscle twitchings occur at times Convulsions are very infrequent There is considerable difference between these symptoms and those usual to the uremia of Bright's disease and there is a considerable interval of time before they do appear This suggests that uremia in Bright's disease is something more than the result of retention of substances normally excreted from the body and that in the pathological processes going on in the body in the presence of severe Bright's disease other toxic substances are generated Various observations as that of Foster[4] fit with this idea Also serum of dogs in advanced uremia has been found highly toxic to the heart of frogs with a digitalis like action Concentrated blood serum from uremic patients causes paralysis and death when injected into mice and rabbits [5] Certain color reactions occur, when the serum of uremic patients are tested [3] [75] These are diazo reactions, modifications of Ehrlich's diazo reaction or van den Bergh's reaction Andrewes [6] describes a useful one of these as does Becher [3] The substances producing these reactions are thought to be of intestinal origin and related to indican Possibly they may be substances not found normally in the body Urine from uremic patients seems less toxic on intravenous injection in animals than is normal urine [11] indicating retention of some toxic substance normally excreted

There seems no question but that numerous of the symptoms appearing in uremia can be caused by retention of various substances, which under normal conditions are in the circulating blood and appear in the urine It is also probable that in the disturbed metabolism of severe Bright's disease substances which are precursors of innocuous end products of metabolism may accumulate and cause toxic responses According to Harrison and Mason in their review of the pathogenesis of the uremic syndrome at the present time it is possible to account for most of the clinical manifestations of uremia on the basis of alterations in the concentration of known compounds in the milieu interieur However there is reason to believe that some and possibly many undefined substances are also concerned In the final analysis the uremic death of the most highly integrated

organism is strictly comparable to the dissolution of the most simple organism in an aging bacterial culture both are destroyed in an environment poisoned by the products of their own metabolism

Circulatory

In a very large number of patients with Bright s disease particularly those with chronic forms there are evidences of disturbances in the circulation of one form or another If edema already discussed under Renal Pathological Physiology is considered a circulatory disturbance then practically every patient with Bright s disease shows evidence of disturbed circulation The disturbances here to be discussed are those associated with the lesions in heart and blood vessels already described in the section on Pathology and in addition increase in blood pressure Circulatory disturbances play a very important part in relation to the symptomatology and the progression of Bright s disease of this there is no doubt The relation of circulatory disturbances to the lesions in the kidney is various some circulatory disturbances are caused by the lesions of Bright s disease some of them cause certain renal lesions which are found in the kidneys of patients with Bright s disease some are merely coincidental Their pathological physiology will be discussed under the headings Blood Pressure Changes and Cardiac Disturbances

Blood Pressure Changes — Blood pressure is elevated in very many cases of Bright s disease in acute Bright s disease high blood pressure is apt to be temporary in chronic Bright s disease usually it is persistent High blood pressure is relatively infrequent in acute Bright s disease occurring usually when renal function is disturbed markedly but some rise in blood pressure occurs frequently during the course of chronic Bright s disease increased blood pressure developing sooner or later in the course of the disease is the rule Clinically there is an antagonism between high blood pressure and edema of renal origin the presence of both at the same time is exceptional both do occur in the Kimmelstiel Wilson syndrome Contrariwise high blood pressure and edema of circulatory failure origin very usually go together How is the elevated blood pressure in Bright s disease brought about? What is its relationship to the renal lesion and the consequent disturbance in renal function?

As we follow patients with Bright s disease in the clinic two very different relationships as to increased blood pressure are obvious One group of patients is seen with definite symptoms and signs of Bright s disease at a time when blood pressure is normal or only very moderately elevated in many of these sustained high blood pressure develops sometimes later to recede but usually to persist unless marked cardiac decompensation ensues Another group of patients are

seen with high blood pressure at a time when there is no, or only slight, evidence of the existence of Bright's disease, in many of these with persisting high blood pressure evidences of the presence of Bright's disease increase. As time goes on, these patients run different courses: one group has increasing evidences of cardiac failure; another group shows progression of symptoms and signs of Bright's disease which finally dominate the picture, although there are some evidences of coincident cardiac insufficiency. In still another group of patients the evidences of Bright's disease remain in abeyance, and their sickness advances along the lines of cardiac decompensation. In all of these patients cerebral vascular lesions may appear before either cardiac or renal insufficiency is very prominent or during the course of either of these routes of downward progress. These patients end their course in one of three ways: uremia, cardiac failure or cerebral vascular accident. In some of the patients combinations of these progressions appear.

A little consideration of the mechanism of hypertension may help somewhat in an understanding of the situation. On theoretical grounds blood pressure will rise either as the result of an increased cardiac output, peripheral resistance remaining unchanged, or as the result of an increased peripheral resistance, systolic output remaining unchanged. Also increase in blood volume and increase in blood viscosity are additional possible causative factors to be considered. While theoretically increased viscosity of the blood usually is considered to be a possible cause of increased blood pressure, it is of great interest that in a clinical condition in which blood viscosity is greatly increased, namely in polycythemia vera, hypertension is the exception, and reducing the viscosity of the blood by therapeutic measures which decrease the blood count to normal does not lower the blood pressure.

For an accurate estimate of effects of increased systolic output, unfortunately we were long handicapped by the lack of any satisfactory method for accurately determining the systolic output or the minute volume of blood in man with different forms of circulatory disturbance. Now with satisfactory methods it has been shown that in man with hypertension systolic output and minute volume remain within normal limits, so long as the hypertension is the essential abnormality[40-42]. Moreover, for a long time the general feeling has been that, since cardiac rate and other evidences of change in cardiac function in association with the earlier periods of high blood pressure are largely lacking, increased cardiac output does not play any important causative part in hypertension. On the other hand, the consensus of opinion now is that high blood pressure is caused mainly by an increased peripheral resistance. Most agree that the change takes place in the small blood vessels and is not related to demonstrable arteriosclerotic lesions in palpable arteries. Measurements of blood volume in hypertensive patients fail to show a consistent increase in patients with uncomplicated hypertension[43-44], and so

plethora can not be a prime cause of high blood pressure The same is true of increased blood viscosity [45]

Although there is a general acceptance of the view that increased peripheral resistance from changes in smaller vessels is the prime cause of hypertension there still is little knowledge of precisely how it is brought about Is it merely the result of maintained contraction of the smaller arteries and arterioles? Is there some change in the vessel wall permanently narrowing the lumen? Does some vascular lesion interfere with vasodilatation? Do the capillaries now known to contract and dilate actively play a part? Quick changes often observed in blood pressure in some types of hypertension give credence to the idea that contraction of the vessel wall often must be a large factor In other patients day in and day out the pressure varies but little and it would seem probable that actual organic lesion in vessel wall must be present Histological study shows that small arteries often are thickened in patients who have had hypertension Direct observation during life of arterioles and capillaries in eye grounds in the skin and in excised muscle and connective tissue point to the occurrence of lesions here This is definite evidence of organic change in the small vessels but these changes in blood vessels do not necessarily precede hypertension Sometimes they appear to do so and sometimes the vascular lesions seem to result from continued hypertension or at least to follow it

Goldblatt [46] by placing a clamp on the renal artery so as to decrease volume of renal blood flow and to decrease the pulsatile element in renal blood flow produced hypertension in dogs and in monkeys and in time lesions of the small arteries and arterioles both within and without the kidney Repetition of these experiments in many laboratories produced the same results This manoeuver according to some produced something [47–48] now variously named renin angiotonin hypertensin to bring about peripheral vascular constriction It has been shown in these experiments on animals that their hypertension is mediated by a chemical or hormonal mechanism not by a nervous mechanism

Not all however agree to the presence in hypertensive patients of a pressor substance Several different observations indicated that the damaged kidney might be responsible for the production in decreased amount or for the failure of production of some substance which under normal conditions antagonizes the pressor mechanism [206, 207] Such an anti pressor factor then by its action would result in an increase beyond normal of blood pressure Extracts of kidney tissue were found to be capable of reducing the blood pressure of animals made hyper tensive and of a few patients suffering from hypertension This idea would make of hypertension a deficiency disease resulting from the failure of the kidney to elaborate an essential constituent whose absence results in hypertension

More investigation is required to determine whether a pressor or an anti pressor mechanism is responsible for the experimental hypertension just described

That the hypertension results from the injury to the kidney of these animals seems proved However, it is well to recall that banding the renal artery is not the only way to cause hypertension in animals Prior to Goldblatt's work hypertension had been produced by subtotal nephrectomy Also it can be produced by wrapping the kidney with cellophane Furthermore various extra renal procedures such as injecting kaolin into the subarachnoid space and the injection into the animals body of such substances as calciferol sex hormones and desoxycorticosterone will cause hypertension So it is obvious that the mechanism of experimental hypertension is not as simple as was thought in the early period following the work of Goldblatt and his associates

If these manoeuvers will produce hypertension in animals, then it is possible that some similar mechanism is operative in the hypertension so often occurring in man In favor of this are (1) the observation by injection methods that flow of fluid through the vascular system of the kidneys from patients, who have had hypertension without renal insufficiency is less than through control kidneys from patients without hypertension[59] (2) the results of tests of renal function using inulin and diodrast which show a relatively high glomerular filtration (inulin clearance) in proportion to total renal flow and tubular excretion (diodrast clearances) which usually are somewhat reduced results which have been interpreted among other changes as indicative of vasoconstriction of the efferent arterioles of the glomeruli[263–66], (3) the demonstration of pressor substances in the circulation of hypertensives[49] similar to those found in animals with experimentally produced hypertension[4–58] (4) the reduction of blood pressure in some humans with hypertension following removal of one diseased kidney[60, 61, 62] and (5) the development of high blood pressure in patients with Bright's disease, whose renal lesions are of a nature to disturb blood flow through the kidney

Doubt however has been registered by various observers as to the validity of some or all of the several items in the preceding paragraph, items which have been cited as favoring the view that essential hypertension in man has the same primal cause and mechanism as that produced in animals by methods reducing renal blood flow As the discussion now stands, in view of the observations cited in the succeeding paragraphs it seems that the primal cause of essential hypertension does not lie in reduced blood flow through the kidney, although it is very obvious that renal lesions do play a part in causing the appearance of the rise in blood pressure that develops so often during the course of Bright's disease and almost always in the later periods of chronic non edematous Bright's disease in which so often it becomes of far greater importance than the renal insufficiency[374], even if the exact origin and mechanism remains uncertain

It is fair to state that in most of the patients who are the basis for the preceding statements hypertension has been present long enough to have led in all probability to the development of lesions in the blood vessels of the kidney, which

may be responsible for the evidences of decrease in renal blood flow Talbott and his associates[60] found a significant correlation between the results of renal clearance studies and the microscopic appearance of the renal blood vessels i e the more severe the renal vascular disease the more reduced the glomerular filtration rate and the renal blood flow which is confirmatory of this idea They found that renal clearance studies gave normal values in 7 of 8 patients in whose kidneys biopsy studies showed no or only very slight lesions in the arterioles although these patients had well developed hypertension with the usual clinical manifestations only with the finding of marked renal vascular lesions was renal blood flow seriously reduced

Dock with Cox[82] by injection methods of the renal blood vessels failed to get a constant decrease in renal blood flow in patients who during life had been hypertensive this adds another element of doubt as to a reciprocal relationship between hypertension and renal blood flow That in man as has been shown to be the case in animals with experimental hypertension produced by a constricting clamp on the renal artery the hypertension precedes organic lesions of the renal blood vessels is confirmed by the observations of Castleman and Smithwick[84] who studied histologically bits of kidney removed from hypertensive patients during the operation of thoraco-lumbar sympathectomy They found grade 0 vascular disease in 7 per cent grade 1 in 21 per cent grade 2 in 25 per cent grade 3 in 33 per cent and grade 4 in 14 per cent of 100 specimens of kidney tissue This is in sharp contrast to the usual finding of well marked renal vascular disease in specimen of kidney from patients dead after having had essential hypertension They concluded from these studies that in man the morphological evidence of renal vascular disease was inadequate in more than half of the cases to be the sole factor in producing their hypertension and that in many of these and probably in others the hypersensitive state antedated the renal vascular lesion which once established probably aggravated the hypertension

The accumulation of many patients with various types of unilateral lesions shows that high blood pressure is a relatively infrequent accompaniment and what is more significant removal of the one diseased kidney from patients who do have high blood pressure often has no ameliorating influence on their high blood pressure This suggests that lesions of one kidney when the other is normal do not have that immediate relationship to high blood pressure as was suggested by earlier studies Mosenthal[3] however has suggested that in this relationship the time element is important According to him the unilateral renal lesion may needs be present for a long time before it will cause increased blood pressure and that its first effect is an intermittent rise in blood pressure which later becomes permanent until reduced by removal of the diseased kidney In support of this he reports a patient who for 37 years had a lesion of one kidney caused by a congenital obstruction at the right ureteropelvic junction from an

aberrant vessel For 6 years she had intermittent rises in blood pressure This then became permanent to be relieved by right nephrectomy, blood pressure remained normal from April '41 to Sept '43 when last observed Mosenthal believes that this sequence may be explained by a compensatory mechanism in the generation of pressor and antipressor substances in the abnormal and normal kidney with the effect of the abnormal kidney finally becoming preponderant This would explain why in some patients with one kidney diseased there is normal blood pressure and in another high pressure If removal of the diseased kidney does not lower blood pressure Mosenthal postulates that in the other kidney or elsewhere in the body there have developed causes for high blood pressure

More extensive studies of renal function in man by means of tests of renal function devised by H W Smith show that in numerous patients hypertension has developed in man at a time when renal function is normal, and there is no evidence of reduced blood flow through the kidney[3, 6] This is in accord with the studies of Talbott and his associates[28] and of Castleman and Smithwick[84], who showed that histological evidences of lesions in the renal blood vessels of man followed rather than antedated the hypertension

Just what inaugurates the change in man, which leads to hypertension, as yet, then can not be stated with any certainty The problem here is in very much the same state as the one concerned in chronic myocardial insufficiency, it is the first step in the mechanism of each of which we know least

As already has been stated in man with Bright's disease there is clinical evidence that in some of the patients hypertension is a sequence to, and probably results from the lesion in the kidney Equally there is clinical evidence that in other patients the Bright s disease develops after the hypertension has been established or while the hypertension is developing In the former hypertension seems caused by Bright s disease while in the latter the two are coincidental or the hypertension is causative of the Bright s disease In those patients in whom Bright s disease has become well established before increased blood pressure appears the pathological lesion in the kidney almost always dominantly involves the glomeruli[2] with lesions of some degree present also in the arterioles of the kidney whether the renal lesion is of the form of a glomerulonephritis, a nephroarteriolosclerosis or a chronic pyelonephritis The histological changes seen in the glomeruli indicate among other disturbances a choking of the glomerular blood flow This is in accord with the results of inulin tests and experimental hypertension all pointing to a decreased renal blood flow as the prime disturbance leading to high blood pressure In the other group in which hypertension precedes or accompanies the appearance of evidences of Bright s disease the subsequent renal lesion is of the nephroarteriolosclerosis type

Cardiac Disturbances — In acute Bright s disease cardiac disturbances are infrequent in comparison with their incidence in subacute and especially, in

chronic cases In the majority of patients with acute Bright s disease symptoms of cardiac insufficiency are absent and physical examination shows the heart to be within the range of normal as to size However in some of the patients with acute Bright s disease there develop dyspnea cyanosis cardiac enlargement with or without systolic apical murmurs and signs of pulmonary and hepatic congestion [6] If roentgenographic and electrocardiographic examinations are made a considerable proportion of these show departures from normal heart size and myocardial activity A rather rare case will die with signs of cardiac failure Edema either pulmonary or peripheral in acute Bright s disease may be the result of either cardiac insufficiency or of renal insufficiency or of a combination of the two In the individual patient it is not always easy to differentiate between circulatory and renal edema

Individual or small groups of patients with evidences of cardiac disease complicating or accompanying acute Bright s disease have been reported by Goodhart Silbermann Hutinel Nobecourt and Voisin Levy Whitehall Longcope and Williams Feller and Hurevitz as referred to by Odel and Tinney [67] Franke [68] found by x ray that the heart had enlarged in 75 per cent of 67 cases of acute Bright s disease Alwens and Moog [69] in 4 cases by x ray demonstrated cardiac enlargement with subsequent return to normal size Guthrie [70] found enlargement in a third of 34 cases Hayman and Martin [71] in half of their patients Rubin and Rapoport [72] in 14 of 57 cases Whitehall Longcope and Williams [73] observed cardiac failure in 71 per cent Odel and Tinney found cardiac involvement in 16 per cent of 136 cases

In the electrocardiograms of patients [74] [6] with acute Bright s disease T wave changes flattening or inversion of T1 and T4 are the most frequent changes As they occur without elevation or depression of the S T segment and without Q wave changes confusion with acute myocardial infarction and with acute pericarditis is avoided

Occasionally the symptoms and signs of cardiac insufficiency are so dominant as to obscure the existence of the causative acute Bright s disease until urine studies have been made Even patients with such marked cardiac involvement may recover with no residual abnormal heart signs or symptoms

The exact mechanism of the cardiac insufficiency is not clear Some of these patients have hypertension others do not There seems no consistent relationship between severity of the renal lesion and the occurrence and severity of evidences of cardiac damage In the relatively few fatal cases with autopsy heart dilatation has been prominent but hypertrophy also exists The valves are normal Histological study fails to show characteristic or considerable myocardial or coronary artery lesions The change would seem related to some toxic effect on the heart muscle a situation possibly not very different from what occurs in the circulatory failure of various acute infectious diseases

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Cardiac Disturbances — In acute Bright's disease cardiac disturbances are infrequent in comparison with their incidence in subacute and especially, in

condition as cardiac enlargement and in the emphysematous chest, where palpation and percussion are rendered inaccurate by increased pulmonary resonance

At some stage in this progressive enlargement the ordinary evidences of cardiac insufficiency begin to appear breathlessness, palpitation precordial discomfort irregularity of rhythm edema congestion of the lungs liver and kidneys etc Extrasystoles occur often while later auricular flutter and fibrillation may develop especially the latter Pulsus alternans is an important index of cardiac failure A systolic murmur at the apex very often appears due to dilatation of the mitral ring In these hypertrophied hearts also one frequently detects at the apex a slight presystolic thrill and hears a late crescendo diastolic murmur or a rumbling quality to the first sound suggestive of mitral stenosis which diagnosis not infrequently is made A different sort of diastolic murmur may appear Just after the second sound in the aortic area or rather more frequently in the third or fourth left interspace near the sternal margin is heard a low pitched blowing murmur almost entirely filling diastole This comes ordinarily, when there are very definite evidences of cardiac insufficiency Both these murmurs the presystolic at the apex and the diastolic at the base are functional and at autopsy no organic stenosis of the mitral valve and no thickening or retraction of the aortic or pulmonic cusps are found The presystolic murmur seems to arise because the left ventricle has an unusually large cavity with relatively shortened chorda tendineae and the diastolic murmur arises from stretching of the aortic or possibly the pulmonic ring (Graham Steele murmur) more probably the former

When cardiac insufficiency sets in urinary output may decrease albumin and casts increase and edema develops When first seen at this stage it is very difficult to determine the type and degree of renal lesion The element of chronic passive congestion usually can be removed by appropriate digitalis therapy and then the remaining evidences of renal insufficiency indicate the type and degree of Bright s disease It is important to realize that cardiac insufficiency along with or even without a slighter degree of Bright s disease may give the urinary findings and functional tests of a marked renal insufficiency the appropriate cardiac therapy in such a patient usually is very effective There is a type of cardiac insufficiency with very marked edema in which an enlarged heart has a slow rate and regular rhythm which with the urine of chronic passive congestion simulates very closely Bright s disease with edema As such cases respond strikingly to digitalis therapy and are little affected by treatment appropriate to nephritic edema it is important to distinguish between the two and digitalization forms the proper therapeutic test

It is important always to keep in mind that in the nephritic patient edema may be either of renal or of cardiac origin In chronic Bright's disease cardiac edema actually is more frequent than renal edema chronic Bright s disease with renal edema, called by some nephrosis is a relatively rare condition while chronic

In chronic Bright's disease[277] cardiac involvement is almost the rule usually associated with high blood pressure In chronic Bright's disease two possibly three factors play a part in disturbing heart function These are increased blood pressure injurious effects of toxic substances on the myocardium and possibly, nutritional changes from disturbed coronary circulation Of these, hypertension is of primal importance although it is possible that the result is not due solely and directly to the hypertension and that the other two factors may play a contributory part At any rate few nephritics without hypertension have cardiac disturbance while almost all with hypertension eventually have it Moreover there seems no doubt but that hypertension may be present for a long time without there being any demonstrable effect on the heart Sooner or later however, cardiac disturbances do arise, and since hypertension is present in by far the largest proportion of nephritics a large percentage of nephritic patients do show cardiac disturbances, and not infrequently these are the chief cause of uncomfortable symptoms

With this development of cardiac symptoms after hypertension has been known to have been present for a varying time, in some patients for a long time it may be argued that the increased resistance against which the heart is working finally proves too much of a load and that the heart, after having at first hypertrophied to do the increased work then breaks down and no longer is able to function adequately with a peripheral resistance that earlier was overcome easily On the other hand, it may be argued that with the changes leading to hypertension disturbances have taken place also in the nutritional vessels of the myocardium, and that a lessened nutrition to an overworked heart muscle results in degenerative changes in the muscle cells or at least, decreased functional efficiency Also it may be that injurious substances associated with the lessened renal efficiency may act directly in an injurious manner on the heart muscle without assuming any vascular lesion to lessen nutrition

However caused the heart in Bright s disease with hypertension goes through the following cycle At first there is no demonstrable enlargement although the apex beat may be forcible and the aortic second sound accentuated often ringing in quality Then the heart enlarges at first towards the left and later towards the right The electrocardiogram will begin to show the curve of left sided muscle preponderance, which increases as time goes on although in a few patients the curve is of the right sided preponderance type or the ventricular deflections are small Enlargement increases and often the area of heart dulness becomes markedly large X ray, of course reveals the hypertrophy and is serviceable in measuring slighter, and recording progressive, enlargement However X ray measurements are rarely a real clinical need since simple methods of physical diagnosis suffice The exceptions lie in the transverse placed heart with high diaphragm in the thick set short chested type, where one may misinterpret the

condition as cardiac enlargement and in the emphysematous chest where palpation and percussion are rendered inaccurate by increased pulmonary resonance

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Bright's disease without renal edema is common, of these latter a large percentage have hypertension and eventually develop cardiac insufficiency with consequent edema of circulatory origin. Circulatory edema usually responds promptly to treatment with digitalis and diuretics, while renal edema is much less affected by this combination. Very frequently such a therapeutic test along with tests of renal function is required to make the differentiation.

The nomenclature of the heart condition associated with Bright's disease is unsatisfactory. The myocardium is the site of the disturbance, and almost always there is both hypertrophy and dilatation of the heart. The valves are normal, there is no pericarditis and as a rule the coronary arteries show no lesion. On the other hand so often the microscope reveals very little or no evidence of lesion either of the muscle fibres or interstitial tissue, that one is not justified in calling it any particular type of pathological lesion. Various terms may be used, "chronic myocardial insufficiency", "hypertensive cardiac disease", "cardiac dilatation and hypertrophy", "chronic myocarditis", "chronic non valvular disease" etc.

Nervous System

As discussed elsewhere under uremia certain nervous system symptoms in severe Bright's disease can be caused by toxic substances retained in the body as a result of renal insufficiency or resulting from accompanying perversions in metabolic breakdown of food and body constituents. With these there are demonstrable no organic lesions of the central nervous system. However many nervous system symptoms appear which are not to be explained on such a toxic basis but which would seem related to lesions of the cerebral blood vessels or to focal lesions of the cerebral tissues. These symptoms are the convulsive seizures, the transitory and persisting focal palsies, monoplegias, hemiplegias, the aphasias and the neuro-psychotic disturbances. Also the headache, the vomiting, the apathy, somnolence and coma, the twitching, the amaurosis and the Cheyne Stokes respiration may be of either toxic or organic origin, probably more frequently the latter than the former. However often gross focal lesions are not found [78], edema may or may not be present.

The symptoms resulting from organic changes in the central nervous system are associated most frequently with hypertension and associated vascular lesions, sometimes with arteriosclerosis without increased blood pressure, both with or without accompanying evidences of Bright's disease, sometimes with edema, focal or general, causative of increased intracranial pressure. At autopsy the brain will show edema, sometimes areas of softening and atrophy, rarely hemorrhages of varying size and a variety of lesions of the walls of the blood vessels, some of which may narrow or occlude their lumens. With deficient circulatory nutri-

tion degeneration of nerve and neuroglia cells develops this may lead to glial proliferation with the formation of focal gliosis small areas of softening or small cysts The lesions of the walls of the blood vessels are like those in the kidney and elsewhere in the body as already described earlier in this section Many include these lesions of the nervous system under the term, hypertensive enceph alopathy

Lesions of the peripheral nerves except those of central origin are very in frequent Almost the only ones noted in our clinical studies are edema hemor rhage and atrophy of the optic nerve chiefly where it enters the eye

A clinical characteristic of the nervous system symptoms are their transitory character, *often with numerous repetitions and almost complete restoration to* normal function between attacks To many observers this means vascular spasm hindering temporarily the circulation to small areas for too short a time to cause persisting damage or only long enough to leave but a slight residium of dysfunc tion Obviously spasm of the vessel wall would accomplish just this and certain observed spasms in the retinal arteries support this view Their frequent occur rence with hypertension predicates increased tonus and irritability of cerebral vessels in hypertension

We have some evidence that this condition is present in blood vessels else where in the body Paroxysmal tachycardia hemianopsia temporary blind ness, fainting epileptiform seizures and memory loss have been observed by me and others uggesting further the possibility of nervous system symptoms from non obstructing vascular disturbances The paucity of focal lesions found in the brains[278] is in accord with a vasospastic cause

This vasospastic explanation however is not accepted by all This group *believes that obstruction in a small artery can lead to focal disturbances of cerebral* function with edema in adjacent tissue and that clearing comes with reabsorption of the edema and bettered nutrition from small collateral vessels coming into function Just such transient palsies as occur in Bright s disease are observed following embolism of small arterial twigs in the brain the emboli coming from thrombi in the heart as in mitral stenosis or from dislodged bits of vegetations from the valves in patients with bacterial vegetative endocarditis The fact that postmortem study of the brains of patients with so-called hypertensive enceph alopathy may show focal organic lesions of one kind or another is not in harmony with the theory of transient vascular spasm as the cause of the nervous system symptoms

Method of Examining the Patient with Bright's Disease

History and Physical Examination

A careful, complete history and thorough general physical examination should be the first step in the study of every patient with Bright's disease. Study of the heart and blood vessels is particularly important. The size and rhythm of the heart should be determined. X ray examination of the heart usually is not needed, for simple methods usually tell us quite accurately its size. When percussion and palpation furnish unsatisfactory evidence of heart size, or when exactness of measurement, particularly in following change in heart size, is desired, the x ray should be used. If x ray examination is made, the tube should be at least six feet from the plate to give parallel rays so as to prevent distortion. Rhythm usually can be analyzed satisfactorily without electrocardiogram, if the examiner understands cardiac arrhythmias. The electrocardiograph, of course, gives more accurate information.

Much can be learned from the study of the pulse. It is most unfortunate that the clinician of today so often has lost the keen touch of the older generation, who had to depend on their simple senses and common sense for so much of their information about their patients. I have been interested to find that at times we can detect a pulsus alternans which tries the patience and technical skill of assistants to demonstrate it with any type of polygraph. The pulse must be studied to determine changes in vessel wall, variations in pulse wave and the characteristics of the rhythm. As stated above, most arrhythmias can be diagnosed with stethoscope and palpating finger. A manometer is needed to record blood pressure; both systolic and diastolic pressure should be recorded. The manometer often will detect a pulsus alternans missed by finger and polygraphic tracing. In fact to recognize pulsus alternans feeling the pulse, use of the manometer and a polygraphic tracing often are needed, for sometimes the one or the other gives the evidence. In using the manometer the auscultatory method is best for pressure determinations; it is well to remember that at times silent zones occur below the actual systolic pressure, and so the true pressure will be missed unless the pressure is pumped up high and observations made of the level of pressure of the first appearing sounds with both a rising and a falling pressure. Such silent zones probably arise from temporary spasm of the wall of the artery.

Ophthalmoscopic examination should be a regular part of the routine physical examination of the patient. Much of the greatest value in diagnosis and prognosis thus is learned. Periodic weighing of patients is important. It gives the best index of variations in edema. It is an indication of the adequacy or inadequacy

of the diet A progressively falling weight when the patient is given a diet of sufficient calories and is not losing edema is a sure sign that the disease is progressing unsatisfactorily

Hemoglobin estimations and red cell counts are other methods of following progression of Bright s disease

Urine Analysis

Much is to be learned from study of albumin content and the casts and cells in the sediment There is a very unfortunate tendency to neglect this especially the latter and to do it carelessly Sediments must be studied in freshly passed specimens for they often disintegrate quickly particularly in alkaline urines The very general custom of having urine sediments examined by technicians probably is the cause for the very general neglect of the valuable information to be obtained from such study If physicians would study the urinary sediments of their patients for themselves instead of having technicians do it they would know vastly more about what is going on No description given you can possibly replace personal observation of casts and cells in the urine The cast and cell picture gives us our most accurate knowledge of the degree of activity of renal disease Glucose should be tested for and the specific gravity taken The latter is very important The twenty four hour amount of urine of patients under study should be measured and recorded The value of this information is enhanced greatly when similar observation of fluid intake is made The important thing to know is whether there is a normal balance between fluid intake and urine output The output of urine should be about two-thirds to three fourths of the fluid intake This varies with temperature for in hot weather much more water leaves the body as sweat

Except for albumin glucose casts and cells specific gravity and amount little else of significance can be learned from the study of the urine Other observations so often reported from laboratories are of no real help in studying the patient with Bright s disease and represent an unintelligent waste of money and energy

Tests of Renal Function

Several tests are worth while carrying out Others may be of use in investigation but add no knowledge of very practical value for the patient with Bright s disease Of course this statement only holds true of present knowledge better tests may supplant these later These tests are (1) a concentration test (2) the phenolsulfonephthalein test, (3) the determination of the total non protein nitrogen or of the urea nitrogen of the blood only one of these two blood nitrogen determinations needs to be used (4) one or several clearance tests

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as within normal limits When separate kidney function is being tested by ureteral catheterization a 15 minute collection is made a 15 per cent excretion for each kidney with first appearance in 5 minutes is regarded as normal

One must remember that there is an inherent error in the test of about 10 per cent This is due to various factors over which one has little control One of the commonest is the inability to exactly match the unknown against the standard In the presence of cyanosis a change takes place in the dyestuff whereby it in part becomes colorless This may be a factor in cardiac congestion in which it is known that the phthalein excretion may be moderately low without any real kidney disease Most important is it to remember that a single determination of the phthalein, except where it is found to be normal is in itself of little value *Repeatedly* lowered phthaleins do however mean something When the intra muscular injection gives unsatisfactory results or when an especial accuracy is needed the dye should be given intravenously

The phthalein test is far from being as delicate as a *concentration test and* therefore is of less value in early diagnosis Again it is far from being as good an index for treatment as the blood urea nitrogen or total non protein nitrogen It is of greater value in prognosis A gradual progressing depression of the phthalein excretion in a chronic case is of grave omen particularly when the level drops below 15 per cent On the other hand one must always bear in mind that occasionally a patient may live for many months with practically no excretion of phthalein Furthermore in an active lesion the phthalein may rise again *from 0 per cent to normal Such happenings have been observed by me*

Blood Urea Nitrogen Determination — The blood urea nitrogen determination has been without any doubt a most eminently useful test of renal function Its great value has been due to its very *general* usefulness for diagnosis prognosis and treatment It is almost the only accepted test that can be done on an unconscious patient suspected of being in uremia What is said about the blood urea nitrogen is of course applicable to the non protein nitrogen A urea nitrogen above 15 mgm per 100 c c in the fasting blood usually means Bright s disease if one can rule out any of the following conditions (1) any condition producing anuria or severe oliguria such as severe acute Bright s disease mercury poisoning extreme cardiac passive congestion bilateral stones etc (2) back pressure destruction of the kidneys by hydronephrosis etc (3) bilateral tuberculosis or other bilateral destruction of the kidneys (4) intestinal obstruction (5) excessive vomiting (6) Addison s disease (7) multiple myeloma (8) severe alkalosis (9) wide spread burns (10) shock (11) severe hemorrhage especially hematemesis (12) diabetic coma In all of these blood urea levels may be high 50 *mgm per 100 c c or even higher* Chronic passive *congestion in cardiac* decompensation may cause a moderate urea nitrogen increase

The following is the best way of procedure If it is not evident that the patient has very mild Bright's disease, the phenolsulfonephthalein test should be done and before breakfast in the morning blood be taken from an arm vein for chemical analysis Urea determination on the whole is the most useful of the blood chemistry procedures and yields perhaps a little more information than total non protein nitrogen However, either is satisfactory If the values for phthalein excretion and blood nitrogen are about normal, a concentration test should be done This may be done at the outset in obviously mild Bright's disease A urea clearance test gives practically useful information in all except the mildest cases and the very severe ones

A single test of renal function may be misleading, by repetition one learns much more for it is the trend of renal function over a period of time that is important in the individual patient Repetition, too, eliminates the errors of faulty technique

With the phthalein test failure to empty the bladder either because of prostatic enlargement or nervousness is the most frequent source of error This easily can be checked by catheterization When there is a considerable discrepancy between blood nitrogen and phthalein excretion values, this should be done Blood nitrogen values are influenced by diet this needs to be kept in mind in interpreting results Also this fact enhances the value of the results as a guide to proper protein intake in the diet and an index of progress in the patient

Phenolsulfonephthalein Test — The phthalein test in my clinic has been a very useful test of function However it is realized that it has been criticized harshly and even abandoned in many clinics However when properly done and conservatively interpreted, it is a very useful test The test is, of course, somewhat more accurate, when done intravenously but it is rarely necessary or desirable to do it other than in the usual intramuscular way Similarly, it is rarely necessary to catheterize the patient except when one suspects a residual urine, or where one by ureteral catheterization is determining the 'divided function' of each kidney However one must remember that an incompletely emptied bladder always will vitiate the test The following technic has been found satisfactory (1) The patient drinks 600 c c of water (2) Thirty minutes later he voids this specimen is discarded (3) At this time 6 mgm of phenolsulfonephthalein is injected intramuscularly or intravenously if there is marked generalized edema the latter is preferable (4) One hour and two hours later the patient voids as completely as possible and the percentage of the dye in each specimen after the addition of 10 per cent sodium hydroxide to bring out a maximal red color is determined colorimetrically At one hour a normal excretion of the dye is 45 per cent at two hours it is 60 per cent When the dye is injected intramuscularly a two hour excretion of 50 per cent may be regarded

as within normal limits When separate kidney function is being tested by ureteral catheterization a 15 minute collection is made a 15 per cent excretion for each kidney with first appearance in 5 minutes is regarded as normal

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Concentration Tests — A concentration test is particularly useful in indicating slighter degrees of renal insufficiency Many of these tests have been described [5] all depending on the principle of finding out by withholding fluid while feeding a rather concentrated diet how high a specific gravity of the urine can be brought about It is stated that, if a urine with specific gravity above 1 026 is obtained renal function is normal, and no other tests are needed In such tests the specific gravity in the presence of albuminuria should be corrected by subtracting 0 003 for each gram of albumin in 100 c c of urine, and readings of all specimens should be made at approximately the same temperature Various concentration tests have been described Some of these in more general use follow

Mosenthal Test — (1) Patient is permitted usual food and fluid intake (2) Collect in one container all urine voided from 8 a m to 8 p m , measure and determine specific gravity (3) The same for all urine voided after 8 p m to 8 a m

Volhard and Fahr Test — (1) Allow no food after evening meal until test is finished except as follows breakfast at 8 a m of dry cereal with sugar, syrup or honey, one egg, toast or bread with butter dinner at noon of roast beef, steak or chops, boiled or baked potato, bread, butter and jam supper at 5 p m of two eggs bread, butter and jam (2) At 8 a m , 11 a m , 2 p m 5 p m , 8 p m have patient void and collect each specimen in a separate container, after 8 p m to 8 a m collect all urine in one container (3) Determine specific gravity of each of these 6 specimens In at least one specimen specific gravity should not be less than 1 025 preferably as high as 1 030 for normal renal function

Fishberg Test — (1) Give regular evening meal at 6 p m with minimal amount of fluid and a considerable amount of protein (2) Discard all urine voided during night save first sample voided in morning (3) Have patient remain in bed for 1 hour and then void, saving sample (4) Have patient get up, after 1 hour s activity void saving sample (5) Determine specific gravity of the 3 samples of urine If renal function is normal specific gravity of one specimen will exceed 1 022

Addis and Shevky Test — (1) Patient abstains from fluid for approximately 24 hours i e , from after breakfast of one day until after arising the next day (2) Urine voided in first 12 hours is discarded (3) Urine voided in next 12 hours i e from 8 p m to 8 a m is collected and specific gravity taken Normal kidneys show a specific gravity above 1 026 95 per cent of normals show specific gravity of 1 028 or higher the average is about 1 032

Clearance Tests — Clearance tests of various kinds have been described Some give an index of total kidney function as the urea clearance Others measure the functional activity of either the glomeruli or the tubules The ones giving index of total kidney function are of clinical value mainly in following kidney function from period to period as an index of progression of disease in it the

ones giving measure of activity of glomeruli and tubules are useful more in the field of investigation The urea clearance test is satisfactory for the first purpose and is in very general use At present the inulin or mannitol clearances seem satisfactory to measure glomerular filtration rate the diodrast clearance to measure tubular function From the values obtained in these tests with appropriate formulas can be calculated glomerular filtration glomerular blood flow the effective renal plasma flow and the maximal rate of tubular excretion Effective renal plasma flow is calculated from the quantity of diodrast excreted per minute divided by the quantity found in each c c of blood plasma The term diodrast Tm or D Tm is used frequently It is obtained by the method described on a later page of this section There seems to be considerable agreement as to the validity of these tests in the earlier stages of renal disturbance but in advanced stages their validity especially the diodrast tests is doubtful

Urea Clearance Test —(1) After an ordinary breakfast the patient is given an additional two glasses of water (2) The bladder is emptied completely by catheter if necessary and the exact time is noted This specimen is discarded (3) Approximately 1 hour later the patient voids the exact time is noted and the volume of this urine specimen is measured and its urea nitrogen content determined (4) 250 c c more water is drunk and blood is drawn for determination of its urea nitrogen content (5) Approximately 1 hour after the second voiding the patient empties his bladder the exact time is noted and the volume of this urine specimen is measured and its urea nitrogen content determined *Calculations* (1) The volume of urine excreted per minute during each of the 1 hour periods is calculated (2) If the urine output is 2 c c per minute or higher the clearance is called maximal and the following formula is used

$CM = \frac{UV}{B}$ where

CM = maximal urea clearance
U = concentration of urea nitrogen in urine expressed in mgm per 100 c c
V = volume of urine excreted per minute
B = concentration of urea nitrogen in blood expressed in mgm per 100 c c

If the urine output is less than c c per minute the clearance is called standard and the following formula is used

$$CS = \frac{U\sqrt{V}}{B}$$

Average normal values are CM = 75 c c per minute
CS = 54 c c per minute

Results are expressed in percentage of average normal values Values of 70 to 130 per cent of the average normal are considered within the range of normal renal function

Inulin Clearance Test[9, 8, 67, 3] — (1) Test preferably is started in morning with patient reclining in bed throughout test Height and weight are recorded for calculation of surface area (2) At 6 30 a m a glass of water is given, and this is repeated every half hour throughout test (3) At 7 30 a m breakfast of ½ glass of milk and 1 slice of toast with butter is given (4) At 8 a m 15 c c blood sample is taken in oxalated tube (5) 10 gm of inulin in 100 c c sterile normal saline solution is given at body temperature intravenously at rate of 10 c c per minute (6) Have patient void 1, 2 and 3 hours after inulin injection Discard first specimen accurately time and measure second and third specimens save these two specimens (7) At 1½ and 2 hours following inulin injection collect 15 c c of blood in oxalated tubes (8) Inulin is quantitated in the 2 urine samples of (6) and the two blood samples of (7) by colorimetric method

Mannitol Clearance Test — In similar technique mannitol may be used instead of inulin as a measure of glomerular function Results between the two differ very little although there is considerable difference in the size of the molecule of each

Diodrast Clearance — To 800 c c of saline are added 12 c c of 35 per cent diodrast solution Immediately after the infusion is started (zero minutes) 13 c c of diodrast solution are injected into the infusion tubing as a priming dose Urine is collected by catheter at 20 22 32 44 and 56 minutes

Diodrast Tm (Tm = tubular excretory mass or maximal rate of tubular excretion) — The infusion tubing is disconnected from the needle the infusion fluid drained to 400 c c 11 5 c c of diodrast are added to each 100 c c of infusion left in the flask, and 26 c c of diodrast are injected into the infusion tubing as a primary dose The infusion is accelerated for a short time to empty the dead space of dilute diodrast the rate then being restored to 4 c c per minute Twenty minutes later (about 79 minutes from commencing the first diodrast infusion) and then at 81, 103 113 115 127 and 139 minutes urine is collected by catheter

In the average normal subject the above infusion will give 1 5 mgm per cent of diodrast between the 22 and 56 minute urine collections and 30 mgm per cent between the 81 and 137 minute collections The iodine is analyzed by Kendall's method (Kendall E C Determination of iodine Jour Biol Chem, 1920 XLIII, 149)

Combined Inulin and Diodrast Clearances — By using 25 c c of 10 per cent inulin solution in the 800 c c of saline above and injecting 15 c c when 13 c c of diodrast are added as a priming dose as described under Diodrast Clearance

inulin clearance can be determined in the same urine collections as obtained for diodrast calculations

General Consideration of Tests of Renal Function — In considering the question of prognosis and the tests of function we must remember that no one test by itself is sufficient and that repetition of the same test from time to time gives one a very much better viewpoint We should also remember that in the presence of an active Bright s disease there is always the possibility that degeneration will cease and repair take place to such an extent that the patient may change markedly or even entirely recover I have seen at least two cases in which the patients recovered even after the physical condition and all tests indicated a very early death With such facts in mind one can say that the blood urea nitrogen is of considerable value in prognosis A level of urea nitrogen under 40 or 50 mgm per 100 c c is of little value in estimating the prognosis of a given case A level between 50 mgm and 75 mgm especially if the general tendency is upwards is of bad prognosis Again if under proper dietetic treatment the level of urea nitrogen cannot be depressed below 50 mgm the prognosis is definitely poor Above 75 mgm the prognosis is as a rule very poor However one must bear in mind that even with a very high blood urea nitrogen a patient may live like some of ours (O Hare [9]) for months or even years

It is probable that the blood urea nitrogen is of greatest service as an index for treatment and the effect of dietary therapy Whenever this substance is above the normal 15 mgm per 100 c c in the fasting individual it is an indication for a reduction in the protein in the diet There are two possible exceptions to this The first is the cardiac muscle failure case in which the increase in the nitrogen of the blood is due to passive congestion of the kidney In such cases *one should reduce the diet as a whole without reference to the blood urea nitrogen* The second exception is in those cases of uremia in which the patient is vomiting and consequently getting little or no food In spite of the very low intake of nitrogen the blood urea nitrogen continues to rise due to the breaking down of the patient s own tissue protein Here the indication is to get into the patient any sort of food that he can retain in order to stop this tissue breakdown In such a case the blood urea nitrogen suggests the need of getting more protein into the patient if possible

Generally speaking it seems best in the usual case of a high nitrogen retention to reduce the protein intake to around 30 grams per day It can be kept at this level until the blood urea nitrogen reaches a normal level After it has been normal for a week or two one can add 5 or 10 grams per day holding the patient *for a week after each addition until the blood urea is determined If the latter* remains normal another 10 grams may be added If it becomes abnormal one must drop back again to the lower level and try an increase at a later date By

following the blood urea nitrogen from week to week in this way, we have the very best index of the effect of our protein dietetic therapy and to a less extent of other forms of therapy No other test is so flexible in this respect

The urea clearance has much the same value but seems little preferable to the blood nitrogen determinations and as it is rather more complex to carry out, it may be dispensed with in the ordinary management of patients with Bright's disease

The greatest usefulness for the determination of the blood urea nitrogen is in conjunction with the phthalein test It has been my practice to do these two tests together once a week in patients under close observation, less frequently in others The combined curves of these two substances from week to week give us more information than either alone in the severe cases with renal insufficiency For example, a case with a phthalein excretion of 10 per cent and a blood urea nitrogen of 50 mgm would indicate that there was still quite a heaping up of urea in the blood stream, which might decrease under further treatment On the other hand a week later that same case might show still a phthalein of 10 per cent but a urea nitrogen of 22 mgm The interpretation then would be that the abnormal storage of urea had been reduced as a result of treatment The phthalein would indicate that the general level of excretion remained about the same, and hence the patient's renal function had not essentially changed

One of the concentration tests is useful until the Bright's disease reaches the stage of fixation of the specific gravity of the urine at 1 010 to 1 012, after which there is no further change in the progression of the disease Consequently the usefulness of concentration tests in following the course of Bright's disease is confined to the earlier stages of the disease They are not useful in acute Bright's disease with oliguria

Clinical Classification

An etiological classification because of the uncertainty of the exact etiology of most cases as has been indicated in the section on Etiology remains for the present impractical in application clinically to Bright's disease A classification based on pathology is feasible and is used by some clinicians that of Fishberg[36] based on that of Volhard and Fahr[294] is a good example of these

Fishberg's Classification

- Benign albuminuria including the orthostatic
- Nephrosis
  - Larval
  - Necrotizing
  - Chronic
  - Amyloid
- Nephritis
  - Glomerulonephritis
  - Focal nephritis
  - Acute interstitial nephritis
  - Pyelonephritis
- Multiple glomerular embolization in subacute bacterial endocarditis
- Essential hypertension including the malignant phase
- The senile arteriosclerotic kidney

However not always can the pathological lesions present in the kidney be diagnosed with accuracy during life and such classifications tend to too great complexity for clinical use For these reasons a clinical classification seems to this clinician[97] more useful in the diagnosis and management of living patients having Bright's disease However very often in using this type of classification the pathological lesions in the kidney can be inferred with a fair to considerable degree of accuracy

A variety of clinical classifications have been offered with a growing tendency to depart more and more from an etiological or pathological basis and to come to a considerable degree of agreement as to the clinical factors basic to such classifications All clinicians have introduced into their classification a subdivision into acute and chronic Bright's disease with many interpolating a subacute form also generally an acute phase or acute exacerbation of chronic Bright's disease is recognized The subacute form is apt to be poorly defined from the acute on the one hand and the chronic on the other while with the clinical features indicative of an acute Bright's disease appearing in the patient who is being seen for the first time it may not be possible to determine until the acute symptoms and signs

subside, and not always even then, whether the clinician is or is not dealing with an acute phase or exacerbation of a chronic process Some cases of chronic Bright's disease progress steadily without the occurrence at any time of acute phases while other chronic cases advance by reason of repeated exacerbations each showing the clinical features of acute Bright's disease, each exacerbation leaving in the kidney an increased number of damaged glomeruli and tubules and a more extensive sclerosis of both glomeruli and interstitial tissue with a corresponding decrease in the efficiency of renal function

From a clinical view point the chief features of Bright's disease are albuminuria, hematuria, edema and hypertension with varying and usually progressing deterioration in renal efficiency except for the absence of the latter in many acute cases which clinically recover completely Using these features, the author has found the following clinical classification of Bright's disease satisfactory

Acute Bright's Disease, Hemorrhagic Type or Type without Nephrotic Syndrome
Acute Subacute and Chronic Edematous Bright's Disease, Nephrotic Type
Subacute and Chronic Hemorrhagic Bright's Disease
Chronic Non edematous Bright's Disease
Certain Special Types of Bright's Disease
- Kimmelstiel Wilson Syndrome
- Bilateral Necrosis of the Kidney
- Traumatic Uremia Crush Syndrome Myoglobinuria
- Hemoglobinuria Blackwater Fever Transfusion Renal Reaction
- Sulfonamide Kidney
- Hepatorenal Syndrome
- Amyloidosis
- Sarcoidosis of Kidney
- Myeloma Kidney
- Renal Cysts and Polycystic Kidney
- Leptospiral nephritis
- The Kidney in syphilis

In some patients the disease begins as acute Bright's disease and, if the process does not heal while in the acute stage progresses to a subacute and then to a chronic form in other patients no acute stage may have been recognized at any time or acute manifestations may have appeared only during the course of the progress of chronic Bright's disease and should be interpreted as acute exacerbations of the chronic process Hematuria is the outstanding feature of the majority of patients with acute Bright's disease and of those in acute exacerbations of chronic Bright's disease extensive edema is the outstanding feature of a lesser number of patients with acute and subacute Bright's disease constituting the nephrotic syndrome, sometimes the nephrotic syndrome becomes chronic

As a rule when hematuria is prominent edema is slight or even absent and when edema is prominent hematuria is absent or slight the two conditions being in a sense clinically antagonistic In the same way renal edema and hypertension are clinically antagonistic An exception to these statements is seen in the Kimmelstiel Wilson syndrome as described in Part II in which hypertension renal type of edema and renal insufficiency with azotemia and uremic symptoms may be present at the same time in patients with diabetes mellitus Furthermore if tests of renal function are used the patients show slight renal insufficiency in the *presence of extensive edema of renal origin and greater often a progressing insufficiency* in the presence of hypertension With marked edema or the nephrotic syndrome tests of renal function show slight renal insufficiency with the tendency to increasing renal insufficiency as the edema decreases and as the edema disappears an increase in blood pressure as a rule takes place The patient who develops uremia usually is free from edema of the distribution characteristic of edema of renal origin but may show the dependent edema of circulatory origin the latter as a rule resulting from cardiac decompensation following hypertension

In view of what has been stated in the preceding paragraph the author regards Bright s disease as a dynamic not a static process and as the patient is followed *a change of his place in the classification should be expected sometimes* but not always the next position being possible of prognostication with considerable accuracy This dynamic attitude is necessary whether consideration is being given to the clinical picture or to the pathological lesion

In the preceding classification the term chronic Bright s disease secondary to pyelonephritis has been introduced Possibly this is not correct and may bring in an element of confusion However this subdivision of chronic Bright s disease is interpolated because the clinical findings are identical with those of primary chronic Bright s disease and *at the time the patient is seen with findings indicative* of Bright s disease all evidences of pyelonephritis and pyelitis may have disappeared and in the history of the patient the suggestion of a preceding pyelonephritis or pyelitis *may be lacking* In numerous of these patients however there is a history of a previous acute pyelonephritis or pyelitis and even in this late stage numerous pus cells or even bacteria may be found in the urine sometimes when there is no history of an acute stage As these patients in their chronic phase are fairly numerous it seems helpful to group them as a form of chronic Bright s disease as has been done in the classification *being used in this* chapter even though acute pyelonephritis is not considered to be a form of Bright s disease

Hypertension develops in many patients with chronic Bright s disease Also there is a form of hypertension which at first shows no symptoms or signs of Bright s disease but in which later on they appear *seen for the first time at this*

subside and not always even then, whether the clinician is or is not dealing with an acute phase or exacerbation of a chronic process Some cases of chronic Bright's disease progress steadily without the occurrence at any time of acute phases while other chronic cases advance by reason of repeated exacerbations each showing the clinical features of acute Bright's disease, each exacerbation leaving in the kidney an increased number of damaged glomeruli and tubules and a more extensive sclerosis of both glomeruli and interstitital tissue with a corresponding decrease in the efficiency of renal function

From a clinical view point the chief features of Bright's disease are albuminuria, hematuria edema and hypertension with varying and usually progressing deterioration in renal efficiency except for the absence of the latter in many acute cases which clinically recover completely Using these features, the author has found the following clinical classification of Bright's disease satisfactory

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- Sulfonamide Kidney
- Hepatorenal Syndrome
- Amyloidosis
- Sarcoidosis of Kidney
- Myeloma Kidney
- Renal Cysts and Polycystic Kidney
- Leptospiral nephritis
- The Kidney in syphilis

In some patients the disease begins as acute Bright's disease and if the process does not heal while in the acute stage, progresses to a subacute and then to a chronic form in other patients no acute stage may have been recognized at any time, or acute manifestations may have appeared only during the course of the progress of chronic Bright's disease and should be interpreted as acute exacerbations of the chronic process Hematuria is the outstanding feature of the majority of patients with acute Bright's disease and of those in acute exacerbations of chronic Bright's disease extensive edema is the outstanding feature of a lesser number of patients with acute and subacute Bright's disease, constituting the nephrotic syndrome sometimes the nephrotic syndrome becomes chronic

Part II

CLINICAL ASPECTS OF BRIGHT'S DISEASE

The clinical manifestations of Bright's disease will be discussed under the following main headings

- Acute Bright's Disease Hemorrhagic Type or Type without Nephrotic Syndrome
- Acute Subacute and Chronic Edematous Bright's Disease Nephrotic Type
- Subacute and Chronic Hemorrhagic Bright's Disease
- Chronic Non-edematous Bright's Disease
- Certain Special Syndromes of Bright's Disease
  - Kimmelstiel Wilson Syndrome
  - Bilateral Necrosis of the Kidney
    - Papillary Cortical
  - Traumatic Uremia Crush Syndrome Myoglobinuria
  - Hemoglobinuria Blackwater Fever Transfusion Renal Lesion
  - Sulfonamide Kidney
  - Hepatorenal Syndrome
  - Amyloidosis
  - Myeloma Kidney
  - Sarcoidosis of Kidney
  - Renal Agenesis and Hypoplasia
  - Renal Cysts and Polycystic Kidney
  - Leptospiral Nephritis
  - The Kidney in Syphilis

The preceding is a clinical classification already discussed in previous pages which the author has found to group patients with Bright's disease satisfactorily from the point of view of their clinical study The temporal subdivision into acute subacute and chronic is convenient in connection both with treatment and estimation of prognosis but the demarking boundaries can not be drawn very sharply and so there are numerous patients with features that make uncertain just whether they should be called acute or subacute or subacute or chronic while the majority of patients can be placed definitely in one of these groups

A definite time of duration can not be stated for acute subacute or chronic A patient at one time acute may continue for a very long time to show the same clinical features should such a patient after a certain length of time be called subacute and if so just when? That is a thing for arbitrary decision by the physi-

later stage, many of these are indistinguishable from cases of chronic Bright's disease in which hypertension is a sequence to the Bright's disease

Special clinical syndromes included in the preceding list, will be described in the next chapter, which deals with clinical manifestations of Bright's disease

In the classification here advocated the *acute focal Bright's disease* of some authors is not included, there being much doubt of this occurring as a definite entity Also the acute degenerative renal lesions, so common in infectious diseases are not considered to be a form of Bright's disease The acute tubular nephritis of some authors is not included as this seems to be a simple degenerative change or is secondary to acute glomerular lesions and so a form of acute Bright's disease other so-called tubular nephritides are regarded as the nephrotic syndrome of Bright's disease and are discussed in that connection So-called amyloid nephritis or nephrosis is regarded by the author as a degenerative process, a form of amyloid disease, and not as belonging to the same category of kidney disease as does Bright's disease The use of the term, nephrosis to include all kidneys in which tubular degeneration is prominent, a term used by some pathologists and some clinicians has not been used, since it brings confusion with the use of nephrosis and nephrotic for those patients in whom edema of renal origin is prominent this author prefers for the latter, nephrotic syndrome, as already indicated

structures show changes and since changes characteristic of the disease occur elsewhere than in the kidneys this author prefers not to use the term acute glomerular nephritis as a name for the clinical disease but to use it as a term for a certain type of pathological change Much the same objection applies to the term acute nephritis Then, the author of this chapter regards as also being acute subacute or chronic Bright's disease certain patients termed by others nephrosis and believed by some of these to show no glomerular lesions only tubular ones these he includes in Bright s disease as one of its types or forms and regards them in pathological terminology as cases of nephritis usually glomerulonephriti

As we study patients with acute Bright s disease two types are observed In one of these the one by far most frequent in its incidence hematuria of varying degree is present with almost no exceptions and while edema almost always develops it has not the peculiarities of that edema which dominates the clinical condition in the other type called by many nephrosis called by me edematous type of Bright s disease or Bright s disease with nephrotic syndrome This first type I prefer to call acute Bright s disease hemorrhagic type or type without nephrosis or acute hemorrhagic Bright s disease

ician Then there are patients chiefly those with extensive, persisting edema, who have the same clinical features from the time of known onset through periods of months sometimes even of years It is difficult to decide, as time goes on, how to group such a patient acute subacute or chronic There is another type of patient that shows very little other than a few to moderate numbers of red blood cells in the urine and continues to do so for a long time Here is the same difficulty of grouping as to acute subacute or even chronic However, with all of these difficulties and uncertainties this grouping into acute subacute and chronic serves a useful purpose

In medicine the terms acute, subacute and chronic, are used also in a sense other than expressing a time relation or the duration of the illness this is a use to express severity and speed of development of illness, a severe fulminating illness being acute in contrast to subacute and chronic This usage of the terms in this sense seems to the author undesirable and confusing in connection with Bright s disease

The clinical classification used in this chapter admittedly is not very satisfactory None of the many classifications which have been suggested for Bright's disease or nephritis seem to him really satisfactory This is so often true of classifications in medicine, because as perfectionists we seek names which accurately depict a disease and its variants and which give us terms one of which we can fit to each individual patient which we study all too often we lack the accurate knowledge necessary for a classification satisfactory in these senses On the other hand if we are satisfied to use a classification only to group patients for convenience of study and for a better understanding of their condition, we are better off with it than if we make no attempts to group them Many classifications in this sense are useful and which to use becomes largely a matter of personal taste based on one s experiences in the study of patients with the disease subjected to classification For this purpose as already stated the classification of Bright s disease here used appears to be satisfactory

ACUTE BRIGHT S DISEASE

Introduction

Acute Bright s disease seems a satisfactory clinical term for the patients in the early stages of Bright's disease a disease defined in the preceding chapter as a disease in which the kidneys show diffuse progressive, degenerative and proliferative lesions a disease however involving the entire body mechanism and not confined to the effects on function of the renal lesions just mentioned Some prefer to use the term, acute glomerular nephritis for these patients Glomerular lesions do dominate in the kidneys of most of these patients but since other kidney

of the various types of renal lesions that occur in acute Bright's disease and their rate and way of progression What still is lacking is exact knowledge of just what the kidney shows in relation to the clinical picture as the disease progresses and particularly as the kidney returns less or more to a state of normality at least of function if not of structure namely of the process of healing

Experimental lesions in animals have helped toward a better understanding of the pathology of acute Bright's disease and especially an understanding of the healing processes which undoubtedly go on in the human kidney although not very evident in human kidneys available for histological study Unfortunately the renal lesions in animals which have been studied most extensively are not caused by agents which play a part in the causation of acute Bright's disease in man Man's kidneys might react differently from those of the animal Actually a given toxic substance will produce quite varying lesions in animals of different species depending on variations in susceptibility and other factors For these reasons it is not safe to transfer directly to man knowledge derived from observations on experimental nephritis in animals although with reservations they can help and have helped in our understanding of Bright's disease in man

The kidney in acute Bright's disease as seen at autopsy usually but not always is larger than normal It is probable that during life these kidneys always are larger than after death this is based on some observations of the kidney at the time of operative decapsulation the Edebohl's operation Increase in size of the kidney of acute Bright's disease is caused by several factors congestion more effective during life than after death edema hemorrhage swelling of cells lining the tubules possible inflammatory infiltration of the interstitial tissue The capsule usually strips easily leaving a smooth surface Color of subcapsular surface and of cut surface varies being uniform pale gray yellowish gray pale grayish brown reddish brown or often mottled red with areas of hemorrhage rarely the kidney is almost uniformly red even it may drip blood from the cut surface The cut surface usually is moist even when not bloody this is true It everts in proportion to the degree of swelling of the kidney As a rule cortex and medulla are well delimited the medullary pyramids being darker and more congested than the cortex Hemorrhagic areas vary in size and shape sometimes they are linear The degree of mottling depends upon the extent of hemorrhage the hemorrhagic areas vary in shape depending upon whether the blood is chiefly in the interstitial tissue the convoluted tubules or the straight tubules in the cortex or in the pyramids Linear hemorrhages usually are in the pyramids Kidney markings may be well preserved or they may be ill-defined with appearance suggestive of a boiled kidney Glomeruli may be visible as small translucent grayish or red points Whereas usually in the gross the kidneys are definitely abnormal in appearance sometimes they look like normal kidneys and it is only after microscopic examination of these that their abnormality is evident

ACUTE BRIGHT'S DISEASE, HEMORRHAGIC TYPE OR TYPE WITHOUT NEPHROTIC SYNDROME

(Acute Hemorrhagic Bright's Disease)

Etiology and Pathology

As discussed in Part I the streptococcus most often is the etiological agent of this form of acute Bright's disease, this is indicated by the great frequency of the antecedent occurrence of an infection or infectious disease in which streptococci are prominent Other bacteria less frequently are causative Clinically the relationship usually is a development of evidences of acute Bright's disease toward the end of or soon following, bacterial infections in the respiratory tract, particularly sore throat Also if a patient has chronic Bright's disease acute exacerbations which are common usually are associated with streptococcic infections, again most frequently sore throat In the case of acute exacerbations of a chronic Bright's disease the acute manifestations of renal disturbance much more frequently appear earlier in relation to the presumably acute infection than is true of primary acute Bright's disease This difference of relationship in time of occurrence of the manifestations of acute renal disease sometimes helps in distinguishing acute Bright's disease from an acute exacerbation of a previously unrecognized chronic Bright's disease These features along with other evidence already noted in Part I make it very probable that the renal lesions of acute Bright's disease develop as an allergic response to the causative organism rather than being caused by the direct action of the bacteria or of soluble toxins produced by them a time interval being necessary between the development of substances by the bacteria and production by them of lesions in the kidneys because the kidney tissues are not injured until they have become sensitized to products formed in the body by these bacteria and time is required for this sensitization to take place

Our knowledge of the lesions of acute Bright's disease in man is most complete as concerns the severe fatal cases in which the kidneys have been submitted to the study of the pathologists as in Case VI on a later page Knowledge of what is happening during life has been obtained from observations of other kind An occasional patient who has died of other cause early in the course of the Bright's disease has afforded opportunity to study the kidneys in the earlier course of the Bright's disease Rarely at operation a bit of kidney has been made available for histological examination Often in a given kidney lesions of differing appearance furnish a basis for a description of the mode of progression of the lesions From material of all of these kinds we have built up a reasonably satisfactory knowledge

variation in mind it is not surprising that in any group of cases a widely varying picture is found so far as glomerular lesion is concerned and many descriptive names are needed to express the pathological changes which are encountered such as were enumerated in the section on Pathology already referred to

As in the glomeruli so in the tubules exudation degeneration and proliferation combine to give a varied picture, the changes now focal now general and diffuse For the tubules proliferation is relatively unimportant in the picture while degenerative changes are prominent leading to hyaline or colloid degeneration fatty degeneration and all gradations from increased granularity of the cytoplasm up to necrosis

As the tubule is complex in structure with different types of epithelium at different levels and a varying affinity exists in the several sorts of cells for toxic substances further complexity and variety of appearance enter on the basis of the distribution of the degenerative changes In the lumen of the tubules gather various products of these exudative and degenerative changes of the glomerulus and of the tubule to form granular detritus and all varieties of casts Globulin excreted through the glomerular membrane in some kidneys may be deposited in the cells of the tubules to appear as hyaline like droplets and in the lumen of the tubules to form some of the casts

In the interstitial connective tissue in the kidney of acute Bright s disease edema hemorrhage exudation of cells or fibrin may occur although as a rule the interstitial tissue shows relatively little lesion as compared with glomeruli and tubules In the same way blood vessels except those of the glomerular tuft show few lesions at least if there are changes our technical methods fail to show them under the microscope

Most of these acute lesions found in man can be reproduced in animals by various experimental methods The same varieties of lesions occur in all sorts of distributions using the same experimental cause Even with a simple soluble chemical introduced by mouth subcutaneously intraperitoneally or intravenously focality of lesion often is prominent showing that a focal distribution by no means disproves the action of a soluble substance reaching the kidney by way of the renal artery This is one of the important facts contributed by the experimental method

In the experimental animal reparative changes in the kidney are prominent Such are not much in evidence in the human kidney of fatal acute Bright s disease This probably in large part is the result of the way our material is obtained namely from fatal cases with a progressing renal lesion and is what should be expected Animal experimentation however makes it probable that repair is an important process also in human Bright s disease at least in recovery from acute Bright s disease and that often structural and functional restoration is well nigh complete

Glomerular lesions are found almost invariably in acute Bright's disease The type of lesion in the glomeruli varies widely (see Figs 8 to 11 in Part I) as already described in preceding pages under Pathology there may be exudation in which serum, fibrin leucocytes and red cells in varying proportion may be found chiefly in the capsular space, or there may be evidence of proliferative changes Some authorities attribute all hematuria in acute nephritis to the escape of red cells through the capillary walls of the glomerular tuft and believe that hematuria indicates a disturbance in the glomeruli, others think the red cells may escape directly into the tubules from the intertubular blood vessels very probably both origins occur Usually however when there is hematuria in Bright's disease, there are glomerular lesions Degeneration plays almost no part in the glomeruli so far as demonstrable lesion is concerned However, some form of degeneration in large part perhaps never to be demonstrable under the microscope, must be present as an important factor in retention within the body of substances that should be excreted or the escape of substances such as albumin and globulin which normally do not escape In other words there is in some kidneys much functional but relatively little structural evidence of degenerative changes in the glomeruli In experimental lesions a hyaline degeneration in the form of fine droplets in the wall of the glomerular loops has been demonstrated[100] This is seen rarely in human kidneys Also in both animals and man a slight, diffuse, hyaline thickening of the wall of the glomerulus occurs Many think this is one of the earliest changes to occur and according to them precedes proliferation of intra or extra capillary cells Thrombosis or embolism of the capillary loops occurs (Fig 16), both are found in patients with vegetative endocarditis and also in those without it

Proliferation is responsible however, for most of the changes that we see under the microscope in the glomeruli Either the endothelial cells of the capillary or the epithelial cells between capillary loops proliferate to form a very cellular glomerulus (Figs 9 and 10) in which the lumen of the capillary no longer is seen and red cells in the capillaries are few or absent or the epithelium of the parietal layer of the capsule proliferates to give crescentic masses of cells occupying the glomerular space (Fig 12) In some kidneys both the epithelial cells just outside the capillary loops and those lining the parietal part of the glomerular space proliferate to produce in places continuity across the usual space of the capsule All of these forms of proliferation may be present in the same glomerulus Many of these changes in the glomeruli are shown in the illustrations (Figs 6–16) in Part I under the heading Pathology

These changes may occur pretty generally in the glomeruli or be present in only scattered ones In other words the glomerular lesion may be focal or general The glomeruli may show the same type of lesion, when lesion occurs or neighboring glomeruli may exhibit much variety of change With these possibilities of

due to pulmonary edema is another first symptom as are somnolence and headache from cerebral edema (2) Urinary symptoms and signs probably most frequently mark the onset Frequency urgency discomfort to pain in the bladder or lumbar regions scanty or high colored to bloody urine constitute these (3) Cerebral symptoms may mark the onset Somnolence and headache already have been mentioned Also there may be vomiting transitory palsies or convulsions This type of onset occurs more often in children than in adults (4) Rarely onset may be with malaise fever even chills general body aches vomiting sometimes epigastric pain How much of this clinical picture is caused by causative infection how much by kidney disease i not easy of determination in each patient but apparently the Bright s disease can be responsible (5) Another and infrequent way of onset is like an acute cardiac decompensation with all symptoms and signs so pointing to disease of the heart that not until the urine is examined is the correct diagnosis of acute Bright s disease made (6) Visual disturbances blurred vision or transitory amaurosis may mark onset but this happens rarely (7) Insidious onset with only slight malaise is not uncommon very soon to be followed by edema about the eyes or elsewhere and urine abnormalities (8) In many perhaps most patients onset is marked by various combinations of the symptoms and signs just enumerated rather than any single one of them having dominance *(9) Finally in many patients onset is so gradual and symptoms* and signs so few that in all probability the disease has been under way for a number of days before the attention of anyone is directed at it and the correct diagnosis is made (10) In some patients in all probability both onset and course are so nearly symptomless that the disease goes unrecognized How often this last happens is not known but such a happening very likely often has been the beginning of what later is a subacute or chronic Bright s disease developing insidiously with no event noted as the mark of its onset Such cases justify the term *latent acute Bright s disease*

Usual Clinical Picture

This can be brought to the reader s attention by describing a few individual patients From the history and clinical course of them the reader can form an idea of wh it may be expected as the usual clinical picture of patients who develop acute Bright s disease

Illustrative Cases

Case I (Fig 26) A young man of 18 (P B B H Med No 10276) had an upper respiratory tract infection which progressed into acute tonsillitis with subsequent abscess formation This part of the disease occupied nearly three weeks At the end of this time

Incidence

Acute Bright's disease a not infrequent disease, is far more common in children and in young adults than in middle life or old age, but it can occur at any age, cases having been observed with first attack past 60 years of age (Fishberg[48]) and forty five minutes after birth (Karsner[30]) the latter obviously an intra uterine development There is some sex dominance, as a rule there is none in children, in whom the disease is most frequent, while in adults males usually somewhat preponderate in some statistics even up to 2 to 1 or even higher Incidence of the disease seems to be related definitely to the incidence of the infections and infectious diseases causative of acute Bright's disease Greater exposure of males to cold and wet with resultant sore throat and more frequent contact with those having upper respiratory infections play a large part in the increased incidence of acute Bright's disease in the male sex

Symptomatology and Physical Findings

The clinical picture of acute Bright's disease varies very greatly from patient to patient The very mild case has almost no symptoms and would pass unnoticed unless attention had been called to the urine by its decreased amount or its color or unless in routine examination of the urine during or subsequent to an infection or infectious disease albumin casts and red blood cells had been found At the other extreme is the very severe sometimes fulminant case with bloody urine in small amount sometimes with anuria, edema of the subcutaneous tissues, cardiovascular phenomena or somnolence or even coma accompanied by muscle twitchings and interrupted by generalized convulsions, all appearing in the course of a very few days sometimes even in only a few hours In between these extremes are all gradations of severity and speed of development with few or numerous symptoms such as are described in subsequent paragraphs

Onset

As with the general clinical picture there is much variety in the character of onset in some onset is insidious in others abrupt onset symptoms may be mild or severe According to the chief features of onset patients with acute Bright's disease can be grouped as follows (1) Edema often is the thing noticed first Most frequently the patient or an observer notes on the patient's awakening in the morning puffiness about the eyes less often swelling of the feet is the first sign observed noted when the patient puts on stockings and shoes, still less frequently edema of the genitalia is the first observed change, very rarely a swollen abdomen first calls the patient's attention to there being something wrong Abrupt dyspnea

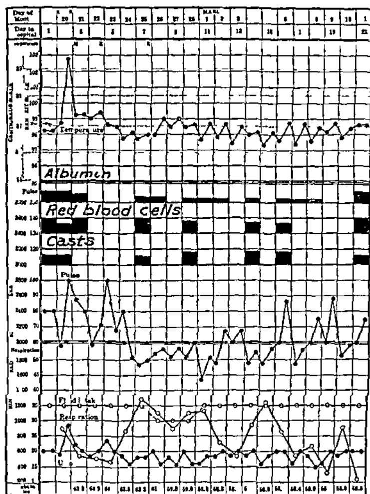


Fig 27 Chart of Case II

urea nitrogen slightly increased (31 mgm per 100 c c blood) the latter decreased (8 mgm) on a diet restricted in protein and rose slightly when the diet contained more protein With subsidence of evidences of tonsil infection tonsillectomy was carried out with this as is usual red blood cells increased in the urine Four months after his first urine examination red blood cells were still present in his urine in small number A year later the patient reported himself as entirely well and again 23 years later

Case II (Fig 27) A young man of 19 (P B B H Med No 8115) had acute otitis media following mumps with a discharging ear for about six weeks prior to the appearance of evidences of acute Bright s disease Before the mumps for nearly three month

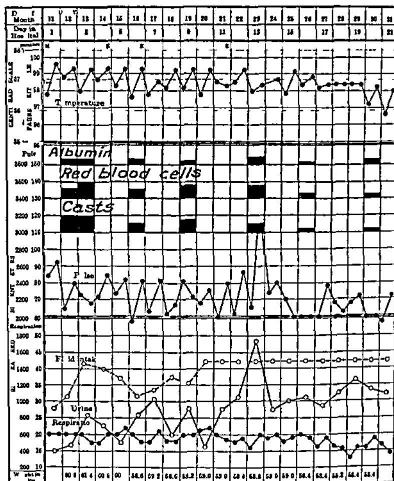


FIG 26 Chart of Case I

the boy's face became puffy The next day he experienced pain in his loins and the day following he noticed that his urine looked bloody By the time he came to the hospital several days later the edema which he had noted in his face had disappeared entirely His tonsils still were swollen and their drainage lymph nodes were enlarged otherwise general physical examination showed no departure from normal findings His pulse was slightly accelerated on admission and his blood pressure was increased to 170 mm Hg systolic There was slight fever lasting a few days slight leucocytosis and no anemia The most prominent disturbance in this boy was in the urine which when he came into the hospital was moderately decreased in amount as shown in the chart (Fig 26) of slightly increased specific gravity (1 025) contained only a slight amount of albumin but numerous hyaline and granular casts a few cellular ones and numerous red blood cells At first phthalein excretion was slightly decreased (42 per cent) and blood

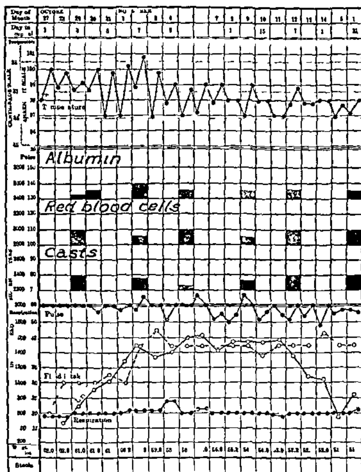


Fig 28 Chart of Case III

amount of albumin many red cells and many granular casts (see Fig 9) the specific gravity ranged from 1 018 to 1 0 8 Phthalein excretion was 60 per cent and blood urea nitrogen 30 mgm per 100 c c of blood Fever was as shown in the chart (Fig 29) With eleven convulsions on the day of admission no more occurred Blood urea nitrogen soon fell to normal and the urine cleared up Three and one half years later the specific gravity of urine was 1 023 and a two-hour test phthalein excretion and blood urea nitrogen were normal but the urine showed a slightest possible trace of albumin rare hyaline casts but no red or white cells This patient may have entered a latent phase to develop eventually chronic Bright s disease He was not seen subsequently

Case V (Fig 30(a)) A young man of 24 (P B B H Med No 4437) had what he termed grippe and two weeks later had pain in his back and noted dark colored urine

he had a persisting cold with rather thick yellowish, nasal discharge The symptoms at the onset of acute Bright s disease were lassitude, headache edema of the face loss of appetite nausea and drowsiness Physical examination showed edema of the face evidences of an inflammatory condition in nose ethmoid sinuses and one middle ear and slight swelling of the cervical lymph nodes Blood pressure was normal there was slight persisting leucocytosis and slight anemia Urine was somewhat decreased in amount with specific gravity of 1 023 and contained very many red blood cells and a moderate number of casts Phthalein excretion was normal and blood urea nitrogen at first was slightly increased later normal The patient s drop in weight of 5 9 kilos in a week (Fig 27) indicates edema was considerable During a two months period of observation red blood cells and casts in the urine decreased, so that at the end of this time they were present in only very moderate amounts Fifteen months later the patient reported himself as being well

Case III (Fig 28) A man of 32 (P B B H Med No 7473) developed malaise and dull headache Six weeks later his throat became swollen and he felt achy all over with high fever and a headache About a week later he noticed that his eyes were puffy and his legs somewhat swollen he had almost constant headache and nausea especially in the mornings After another week had elapsed these symptoms became more severe and in a few days he noted a decrease in the amount of his urine which now was dark brown in color and cloudy Physical examination now showed moderate edema of face and legs and slight tenderness in the flanks and costovertebral angles There was slight fever (Fig 28) leucocytosis to 19 700 and moderate anemia (r b c 3 800 000 and hgb 75 per cent) Blood pressure varied from day to day 140/85 148/96 122/68 134/88 160 70 gradually returning to normal Urine was decreased in amount with a specific gravity of 1 015 moderate amount of albumin and many casts and red blood cells as shown in Fig 3 Phthalein excretion was moderately decreased (38 per cent 44 per cent) blood urea nitrogen was increased to 78 mgm per 100 c c of blood Fever was as shown in the chart (Fig 28) In the hospital casts and blood in the urine decreased phthalein excretion rose to normal and blood urea nitrogen dropped to normal with at first a tendency to rise moderately with increased protein in the diet One year after onset evidences of Bright s disease persisted but six months after this there were no signs of renal lesion urine was free of cells and casts specific gravity was 1 025 phthalein was 67 per cent, and blood urea nitrogen was 11 mgm per 100 c c of blood

Case IV (Fig 29) A boy of 14 (P B B H Med No 3876) had seemed nervous and irritable with other children for one month Fifteen days ago he began to seem drowsy and showed a tendency to sit around and read Ten days ago a swelling in the neck near the ramus of the right jaw was noted and his physician said he had a sore throat He recovered and seemed normal but three days ago his face and eyes swelled and his face seemed drawn to the right Urine was the color of coffee and very cloudy This morning he began to vomit and his muscles twitched he had two convulsions before coming to the hospital and nine more shortly after admission which seemed to start in his left hand with his head turning slightly to the left They did not become generalized He was stuporous his eyebrows and hands twitched his face was pale and very puffy his blood pressure was 160 mm Hg systolic and 90 diastolic His urine was smoky and contained a large

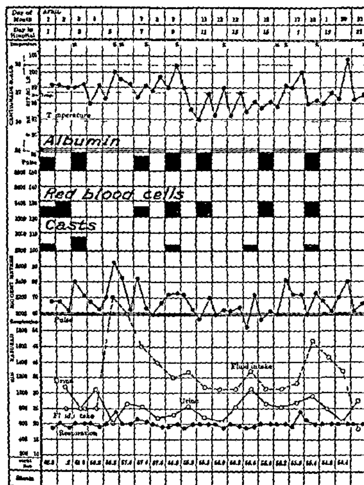


FIG 30(a) Chart of Case V

60 mgm per 100 c c and phthalein which had been 90 per cent dropped to 20 per cent and continued low while his condition was improving but later rose toward normal Three and a half years later although his urine showed a little albumin rare red blood cells and numerous hyaline casts physical examination was negative and blood pressure was normal phthalein was 60 per cent and blood urea nitrogen 18 mgm per 100 c c of blood Seventeen years later the urine had a specific gravity of 1 0 0 with the lightest possible trace of albumin The blood pressure was 130 68 and 144 92 A little later in this year there was no albumin occasional casts and white cells The blood pressure was 120/80 The patient continued to have not infrequent upper respiratory tract infection some with tonsillitis and 19 years after his admission to the hospital with acute

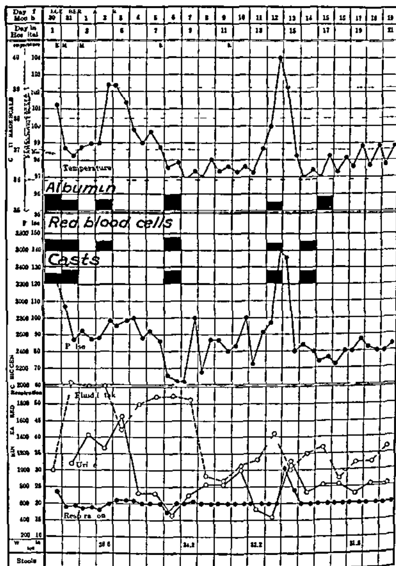


FIG 29 Chart of Case IV

and swelling of the face and legs On admission April 1 1916 his urine was smoky with many red blood cells and a rare granular cast a specific gravity of 1 008 1 011 1 014 over a period of a month and a half (See Fig 30(a)) Four days after admission he complained of mild headache which later became severe and constant, but there was no dyspnea or muscle twitchings His blood pressure rose from 150/92 to 180/112 when the headache was very severe and the patient was mildly delirious not recognizing persons about him later he had generalized convulsions The next day he had no headache was rational and had no more convulsions Blood urea nitrogen was

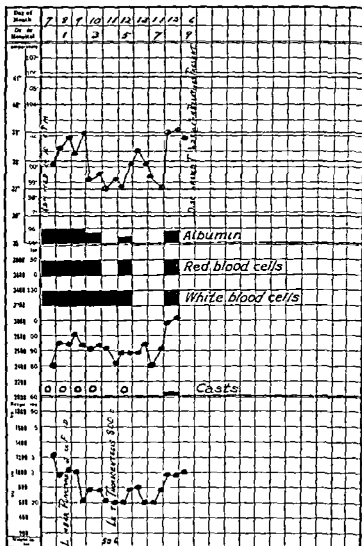


FIG 30(b) Chart of Case V

ous pericarditis hydrothorax left ascites 300 c.c. fibrinou and fib ou pleuritis infarcts spleen recent and old

Kidneys — The left kidney weighed 220 grams and was of normal shape The right was approximately the same weight as the left Perirenal fat was somewhat more edematous than u ual but was not abnormal in amount and not unduly adherent to the kidney Capsule was very thin only slightly adherent it stripped leaving a somewhat shiny

Bright s disease he was readmitted with acute tonsillitis At this time his first urine specimen showed a specific gravity of 1 022, a slight trace of albumin and 2 to 3 red cells and 3 to 4 casts per field, but 5 subsequent urine examinations showed specific gravity of 1 010 and no albumin and no red cells his phthalein was 45 per cent and blood urea nitrogen 11 mgm per 100 c c His urine by a concentration test only reached a specific gravity of 1 026 Soon after this his tonsils were removed with the pathological diagnosis of chronic tonsillitis with fibrosis The patient has not been seen since then It would seem that very slowly he may be developing a chronic Bright s disease, but yet after 19 years he has no clinical evidences of its presence

Case VI (Fig 30(b)) A man of 42 was admitted to the hospital on March 7 1931 (P B B H Med No 38620) with complaint of hematuria of 4 days duration and delirium for 1 day He had according to his brother never been sick before this illness Two weeks ago patient had a cold of moderate severity for which he remained at home in bed for 2 days then he returned to work but 8 days ago he came home from work feeling somewhat played out he went to bed early Next day he had vague aches in shoulders back chest and legs 5 days ago he felt better and was out of bed around the house in the afternoon Four days ago he felt worse his right ankle was swollen but not red or tender for the first time he noted that his urine was slightly reddish His temperature was 101° F His urine got darker and 2 days ago seemed bloody He complained now of some soreness in right side of his throat and yesterday his face became quite swollen

Physical Examination — A well developed well nourished man was restless, thrashed about wildly and was delirious and disoriented There was slight soft pitting edema of the lower back and legs Fundi of eyes appeared normal Lips were dry and encrusted with sordes teeth were in miserable condition Heart was normal on physical examination Lungs showed dulness over left lower half with absent breath sounds below but harsh to bronchial sounds toward midscapular region There were numerous fine crepitating inspiratory rales Rest of physical examination was normal Blood pressure was 170 mm Hg systolic 90 diastolic Temperature was 100 2 F pulse 80 respiration 36 later temperature rose to 102° F (Fig 30(b)) X ray of chest showed consolidation and fluid over lower half of left chest and slight clouding of right lung with small amount of fluid in right costophrenic angle

Urine was reddish brown cloudy alkaline with specific gravity 1 005 a large amount of albumin and a sediment loaded with red cells and leucocytes but no casts Urine continued thus with specific gravity 1 005 to 1 010 but no casts until day before death when a few coarsely granular brown casts were seen (Fig 30(a)) The 1st and 2nd urine were alkaline while 4 more were acid Red blood cells were 3 300 000 leucocytes 12 000 rising to 24 900 Hemoglobin was 85 and then 60 per cent Blood urea nitrogen was 25 mgm per 100 c c rising to 42 mgm and 89 6 mgm (on day of death) Left thoracentesis yielded 800 c c serosanguinous fluid of specific gravity 1 010 containing 800 white blood cells mostly lymphocytes and 45 000 red blood cells per cu mm Total plasma protein was 6 with albumin 2 6 and globulin 3 4 Patient died at 1 48 P M on March 16 1931

Autopsy — Diagnosis acute glomerular nephritis pneumococcic lobar pneumonia right vegetative endocarditis pneumococcic small vegetation on mitral valve fibrin

In Nov again in the hospital blood pressure was 220/190 eye ground changes were more marked but there were no hemorrhages There was very slight anemia no nitrogen retention urine specific gravity 1 020 to 1 013 with a few red and white cells and occasional hyaline granular and cellular casts

In Feb 1934 there was very severe headache followed by generalized convulsions On third hospital admission in Feb 1934 blood pressure was 240/1,0 Now eye ground showed hemorrhages in addition to other changes seen previously Urine had specific gravity 1 024 a very slight amount of albumin with no cells and no casts in the sediment No increase in blood urea nitrogen occurred Phthalein excretion was 35 per cent in 2 hours There was no anemia On Apr 19 left 7th nerve palsy developed On Apr 26 he became stuporous with labored breathing and died

Autopsy showed chronic glomerular nephritis cardiac hypertrophy and cerebral hemorrhages For other details see Case XV on a subsequent page in the discussion of Chronic Non edematous Bright s Disease

Summary of Clinical Picture in Illustrative Cases — The acute phase of disease in these patients has varied in character and severity This seemingly has had little influence on the subsequent course of the disease beyond that those most severely ill are the ones most apt not to survive the acute phase A few die in the acute phase of the disease (Case VI) Very many recover from the acute phase of the disease some to have no subsequent evidences of Bright s disease (Cases I II and III) Some patients continue to have albumin and casts in their urine (Cases IV and V) over a long period of time without ever developing clinical evidences of chronic Bright s disease Some patients after a long period of time of latency of process during which period only the urine remains abnormal progress into chronic Bright s disease of the non edematous type Some patients never become clinically well and their urine continues to be abnormal as time goes on sometimes in a relatively few months sometimes in a much longer time they become patients with chronic non edematous Bright s disease (Case VII) Progression of disease in patients who do not recover from the acute phase of their Bright s disease may or may not be punctuated by acute exacerbations of renal process during which they show the urine changes and symptoms similar to those of acute Bright s disease of the hemorrhagic type

As an Acute Infectious Disease

Edema and hematuria are the features observed most commonly by both patient and his physician in an attack of acute Bright s disease of this type With these usually goes a feeling of malaise often accompanied by fever leucocytosis indefinite body aches and moderate to severe headache suggesting that acute Bright s disease is a form of acute infectious disease not merely a kidney disease an acute infectious disease often progressing to chronic sclerosing kidney lesions as time goes on Someone has pointed out its analogy in these respects to rheu

moderately soft surface of mottled red and reddish gray color On section the cut surface bulged markedly and was moderately soft and uniform in consistency Cortex was of the same mottled red and reddish gray as described previously The normal markings of the cortex were obliterated The medulla was of a dark blackish red color while the line of demarcation between the two was fairly distinct as to color but was not sharp The cortex varied from 8 to 9 mm in thickness The pelvic mucosa showed diffuse congestion and numerous small to medium sized submucosal hemorrhages The ureters were not remarkable Under the microscope the kidneys showed a marked acute diffuse glomerular nephritis The capsule was thin edematous loose in texture containing a few inflammatory cells Glomeruli all showed striking involvement including proliferation of Bowman s capsule into the capsular space and increased swelling of endothelium Associated with the latter were moderate numbers of polymorphonuclear leucocytes within the capillary tufts but strikingly few red cells were in the capillaries The endothelial cytoplasm was swollen containing hyaline granules In the glomerular space in some places there were hemorrhage and fibrin In others numerous polymorphonuclear leucocytes were seen Infiltrating polymorphonuclear leucocytes were quite striking in some of the crescents formed by proliferation of the epithelium of Bowman s capsule Tubules showed a marked thinning of the epithelium in the convoluted portions The nuclei in some instances were pale and washed out suggesting necrosis others contained hyaline granules In the lumen of the tubules were seen leucocytes fibrin, red cells fine brown granular casts the latter particularly in the collecting portions Stroma throughout was slightly edematous with some collections of plasma cells and lymphocytes mixed with a few polynuclear leucocytes In the interstitial tissue recent hemorrhages were present and also occasionally were seen some areas infiltrated with pigmented phagocytes indicative of older hemorrhage No significant vascular changes were noted A very rare glomerulus was atrophic in small fibrosed areas except for this all the features were those of an acute glomerular nephritis

Case VII * — A man of 18 previously always well had a severe cold about Dec. 10 1930 and one week later noted moderate edema of ankles and face followed by nausea, vomiting and bloody urine On Jan 10 1931 he was admitted to the Peter Bent Brigham Hospital Med No 38273 He looked pale and pasty there was moderate ankle edema His heart was slightly enlarged with a systolic murmur at the apex Blood pressure was 162 mm Hg systolic and 105 mm diastolic His eyes showed only slight haziness of one side of optic disc Urine showed specific gravity of 1 032 later decreasing a considerable amount of albumin many red blood cells numerous white cells and numerous hyaline finely and coarsely granular and blood casts Blood urea nitrogen was 32 mgm per 100 c c phthalein excretion was 22 per cent Blood plasma protein was 4 5 gm with albumin 2 4 and globulin 2 1 There was moderate anemia

In May 1933 morning headaches with nausea and occasional vomiting began Blood pressure rose to reach 230 mm Hg systolic and 154 mm diastolic in Oct 1933 In Sept 1933 ophthalmoscopic examination showed tortuosity of vessels and cotton wool spots

* Further description of this patient appears as Case XV on a later page in the description of Chronic Non edematous Bright s Disease

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matic fever which is an infectious disease causing disturbances of wide distribution in the body not merely an arthritis, and, as a rule progressing to chronic cardiac decompensation with deformities of the heart valves caused by a sclerosing process resultant from the earlier rheumatic inflammatory lesions in them This concept of acute Bright s disease as an acute infectious disease gives a rationale for most of the symptoms such as malaise, fever, leucocytosis, body aches gastrointestinal disturbances headache stupor coma, irrationality, all of which are encountered in many patients with severe acute infectious disease of any sort and of any etiology The disturbances in renal function and in the excreted urine may be considered to be the result of the localization in the kidney of severe disturbances caused by this infectious disease In a sense the renal lesions are a dominant feature in this particular infectious disease causative of a number of the features that go to make up the clinical picture of acute Bright's disease, just as in rheumatic fever the cardiac lesions are he dominant and serious features of that disease

Some Unusual Clinical Pictures

Before discussing more in detail the various individual symptoms and signs of acute Bright s disease it will be useful to the physician to cite some of the more unusual clinical pictures of acute Bright s disease some of which already have been mentioned in the section on Onset These are the patients who at first may not be recognized as primarily suffering from acute Bright s disease

Sometimes the clinical picture is one of suddenly developed cardiac decompensation with dyspnea pulmonary edema cyanosis and tachycardia There is no apparent cause for this sudden cardiac failure and yet clinically that seems the situation until the urine is examined and found to be scant and bloody, with albumin and granular casts The subsequent course makes it clear that the renal lesion in some way has been causative of the seemingly primary cardiac decompensation suggesting a marked diffuse myocardial lesion a cardiac disturbance which disappears completely if the acute Bright's disease subsides

Visual disturbances including blindness may be the earliest feature with nothing to suggest Bright s disease until the urine is examined If with visual disturbances go headache and somnolence brain tumor is simulated In some of these patients with the preceding symptoms there is nausea accompanied or followed by vomiting to suggest increased intracranial pressure as from a tumor In some patients with acute Bright s disease convulsive seizures and/or transitory palsies suggest at first either brain tumor or some form of encephalitis These patients may show edema of the optic nerve head papilledema, when the eye i examined with an ophthalmoscope

Occasionally there is fever malaise nausea and headache so marked as to

give the clinical picture of an acute infectious disease In the days when typhoid fever was frequent patients with acute Bright s disease of this type have been mistaken for typhoid fever until repeated urine examinations made it clear that the hematuria albuminuria and cylindruria were other than that common to typhoid fever and other infectious diseases

In an occasional patient with unusually severe pain in the back hematuria and a considerable number of leucocytes in the urine the condition has been mis taken at first for some one of the inflammatory or neoplastic lesions of the kidney Another unusual group of findings has been severe hematuria and rapidly progressive renal insufficiency with very little edema and normal blood pressure

Fahrberg cites a patient whose only complaint was that he had not urinated at all for a week but otherwise felt well There was marked nitrogen retention but no hypertension and no edema With persisting anuria two days later de capsulation was carried out a small bit of kidney showed acute glomerulonephritis Anuria persisted and death from uremia occurred on the fourteenth day The diagnosis of acute glomerulonephritis was verified at autopsy

Such are some of the unusual forms that acute Bright s disease may present and for a time lead the clinician astray in diagnosis

Special Features

Edema

Edema varies greatly in extent in different patients with acute Bright s disease rarely none is observed Most often the patient or his friends notice pallid puffiness of the face (present in 40 of 45 cases showing edema in an analysis of acute cases at the Peter Bent Brigham Hospital) especially about the eyes and over the cheeks very often the patient awakes some morning with this as the first evidence of disturbed renal function so-called *nephritic facies* With extreme edema of the lids lachrymation may be found Sometimes edema about the eyes may be the only noticeable edema (9 out of 40 cases with edema of the face) and it may persist merely for a day or two Quite often however there is demonstrable edema of the lower legs (5 out of 40 cases) especially just above the ankles sometimes over the shins or thighs or when the patient has been in bed at the time of onset of the Bright s disease edema of the lower back and buttocks Edema of the genitalia particularly in the loose scrotal tissues may appear first Edema usually is more extensive than that which can be demonstrated by eye or hand as shown by decrease in weight with increase in urine flow when the patient improves (see Case II) In some patients increase in weight up to 6 or 8 pounds precedes demonstrable edema Very rarely increase in weight is the only evidence of the edema

From slight degree of transitory edema there are all gradations to a rapidly or gradually extending edema which ends in extreme degrees of anasarca giving to the patient a typical pale, pasty appearance with pitting edema, usually soft in character, distributed over the entire body. In these patients with very marked edema the edema is most extreme in dependent parts and in loose areolar tissues such as that of the genitalia and below the eyes. Where most marked, the edema causes distention of the skin producing a glossy, tightly stretched appearance. However it is rare in acute Bright's disease, here under discussion, to have such marked edema with actual rupture of the skin or any very great discomfort from the edema of subcutaneous tissues such as occurs in cardiac disease and in the edematous or nephrotic type of Bright's disease. It is very exceptional to have the hard or brawny edema so common in circulatory disturbances. When edema of the subcutaneous tissue is marked there is often demonstrable fluid in the body cavities sometimes this appears when subcutaneous edema is slight or even absent.

The edema of acute renal disease in distribution is clinically much less related to the effects of gravity particularly in its incipiency than is the case with the edema of cardiac insufficiency. Again in renal edema accumulations of fluid in the body cavities are much less extensive in proportion to edema elsewhere and later in occurrence than with circulatory edema. On the other hand, an occasional case with apparently good circulation has a disproportionate amount of ascites or hydrothorax.

Edema when it occurs in acute Bright's disease and is at all extensive probably affects body tissues very generally but there may be very considerable variation in the degree of edema in different organs, giving different symptoms depending on the structures involved. Some of the pulmonary and cerebral symptoms may be due to such local edema. The same explanation is given at times for gastrointestinal symptoms. In general the edema of acute Bright's disease causes few if any symptoms. Its chief importance lies in its being a significant sign to point to disease in its usual distribution in acute Bright's disease it points directly to that possibility, a possibility speedily to be checked by examination of the urine.

Acute edema of the glottis is described in acute Bright's disease although in all probability in most cases this is an inflammatory edema resulting from a concomitant infection. Such an inflammatory edema may be extremely sudden. The author has seen a patient apparently quite comfortable and free of throat symptoms die of suffocation in five minutes or less in whom the tissues of the glottis and epiglottis were enormously swollen of a gelatinous appearance and showed under the microscope connective tissue fibers widely separated by serous exudation containing extremely few leucocytes but many chains of streptococci. One would fancy that such an inflammatory condition usually is responsible for

the acute edema of the glottis attributed to Bright s disease In other cases an angioneurotic edema may be the real cause

Decreased renal function in certain cases may be related to edema of the kidney Suppression of urine sometimes receives this explanation particularly where it is unaccompanied by any other very marked changes in the urine such as considerable hematuria cylindruria and albuminuria

The electrolyte composition of edema fluid in acute Bright s disease as to kind of substances resembles that of blood plasma although the amount of each constituent may not be the same in the two fluids Different investigators however are not in full agreement as to which constituents are in exce s in the two fluids In general the differences found are small and the significance of these differences probably is not great Non protein nitrogenous constituents have about the same concentration in each The protein content of edema fluid of acute Bright s disease is much less than that of blood plasma it averages 0 4 gm per 100 c c according to Warren and Stead[311 312], which is several times the amount found in the edema fluid of the nephrosis syndrome which varies between 0 1 and only a few hundredth of a gram per 100 c c while the amount in the edema fluid of cardiac decompensation is intermediate to these two averaging 0 24 gm per 100 c c

The pathological physiology of edema is discussed in a preceding section, the reader is referred to that discus ion (see Part I)

Urinary Disturbances

The daily excretion of urine almost always is decreased in the active stage of acute Bright s disease Rarely no decrease occurs The decrease varies from a moderate one all the way to marked suppression and in some patients to complete anuria In the majority of the patients daily urine excretion ranges from 400 to 700 c c In the period when edema is developing oliguria is accompanied by an increase in specific gravity of the urine roughly inversely proportionate to the amount of urine excreted Specific gravities of 1 022 to 1 032 are usual Later when renal function is more impaired specific gravity falls with readings about 1 015 sometimes as low as 1 010 even though edema persists Obviously in a period of diuresis specific gravity falls When edema has decreased and the patient is improving specific gravity returns to average normal levels It is to be remembered that marked albuminuria increases the specific gravity of the urine a 1 per cent albuminuria increase the specific gravity by 0 003 However unless albuminuria is very marked 1 to 2 per cent as occasionally occurs the variation in specific gravity of the urine caused by urinary protein plays very little part in the changes in specific gravity observed in acute Brigh s disease Ordinarily in acute Bright s disease albumin in the urine averages 0 2 to 0 4 per cent too little to have any significance in increasing specific gravity

When the urine is markedly decreased, often there is discomfort in the bladder region with a frequently repeated desire to void These disturbances do not seem to be due to bladder or urethral inflammation but to irritation from the increased concentration of the urine or from increased acidity of the urine Rarely these symptoms are marked enough to suggest cystitis The urine usually shows an increased acidity, if the hydrogen ion concentration is measured colorimetrically, or other method is used to determine acidity

Blood in the urine is a cardinal sign of acute Bright's disease whether in a previously normal kidney or one with a coexisting chronic Bright's disease although often it is insufficient in amount to cause a gross hematuria Cases of acute Bright's disease do occur without blood in the urine although they are rare The degree of hematuria ranges from one only detectable by the microscope after centrifugalization to one where the urine is grossly bloody Usually the blood is somewhat changed so as to give a turbid, smoky appearance rather than the bright red of ordinary hemorrhage Some to much hemolysis of the blood cells may occur to give a varying amount of hemoglobin in solution in the urine, this occurs especially when the urine is alkaline in reaction Rarely there is only hemoglobinuria instead of hematuria Blood in the urine may be but temporary, or it may persist for months finally to disappear entirely and the renal lesion completely heal Under the microscope urinary sediment shows normal looking red blood cells crenated ones or cells which have lost part or all of their hemoglobin the last appearing as cell shadows

The greater part of the blood in the urine is derived from damaged glomeruli Some is the result of hemorrhage into the tubules from the intertubular blood vessels

There may be no very close parallelism between the degree of hematuria and the severity of the patient's symptoms and other signs of illness The amount of blood however does, in a rough way mark the acuteness of the process for most patients An exception may be made to this for cases of embolic glomerular lesions as pointed out by Rochs[313] where a reappearing hematuria may be the sign of re establishment of glomerular circulation and so an indication of improvement

Albuminuria too is an almost constant feature of acute Bright's disease and yet cases are reported of acute nephritis with autopsy confirmation of the lesion, devoid of albuminuria Such I have never seen In war conditions Franke[314] described acute Bright's disease without albuminuria or acute functional renal adynamie where without casts or albumin in the urine soldiers developed a soft painless, rapidly progressing edema general and pulmonary without signs of cardiac failure and apparently when the patient was in a state of good nutrition Still I must confess to skepticism in regard to many of these being actually cases of Bright's disease

The amount of albumin present in acute Bright s disease varies from a very small amount to one which when precipitated almost solidifies the urine As a rule however the amount of albumin in it is moderate 0 2 to 0 4 per cent The degree of albuminuria is not so good a measure of the severity of the disease as is its persistence provided it is not of orthostatic type along with evidences of the patient s renal function and general condition

In acute Bright s disease the protein in the urine is preponderantly albumin with some globulin The nature of urinary protein and its origin will be found discussed in Part I

Fibrinuria is a rare accompaniment of Bright s disease In this condition fibrinogen is present and this results later in a coagulum of fibrin The clots may form before or after the urine is excreted In a study of this O Connor[315] found in the literature two cases of fibrinuria where the condition appeared in individuals treated by plasters of cantharides probably causing an acute Bright s disease from renal irritation in one case possibly the acute Bright s disease of pregnancy in one case possibly an acute Bright s disease associated with a tuberculous suppurating joint in one case possibly an acute Bright s disease associated with influenza and in four cases of chronic Bright s disease

Casts though sometimes absent are found almost always in acute Bright s disease When not found at times this is due to the fact that they disintegrate rapidly and are replaced by a granular detritus having the same significance as casts This may happen if the specimen is not examined soon after it is passed particularly if the urine is alkaline Casts are of all varieties in acute Bright s disease It is worthy of emphasis that many hyaline and even fatty casts may be found without there being any evidence at all of an underlying chronic renal process Showers of casts occur at times in acute Bright s disease with intervening periods of relatively few casts A study of the number and types of casts i of much help in estimating the activity of the renal lesion It is not certain however how far casts when abundant serve to indicate lesion of the tubular epithelium rather than of the glomerular structure According to Cushny s[10] view the matrix of casts originates in material which has escaped from the glomerulus while granules cell debris and cells come for the most part from the tubules Based on this theory if the latter (granules cell debris and cells) are abundant one can infer that there is a considerable tubular lesion in addition to a slight to marked glomerular lesion

Renal epithelial cells and leucocytes usually are found in the urinary sediment in acute Bright s disease At times these cells are very abundant It should be emphasized that the same type of rather small epithelial cells may originate in any part of the urinary tract when present in the urine it is not possible to say whether they come from renal tubule from ureter or from bladder Leucocytes may be abundant when there is no evidence of cystitis or pyeliti They are of

renal origin in these patients, and they may dominate the sediment in some cases of nephritis so that little else is found

The output of nitrogen varies in acute Bright's disease In some patients as measured by the non protein nitrogen or urea of the blood, there is a very considerable retention, and with this there is a decreased amount of nitrogen in the urine Nitrogen retention is most marked in patients with continued oliguria and reaches its highest figures when, as sometimes happens, there is prolonged anuria In severe cases there may be a definite nitrogen loss, if the nitrogen balance is determined there will be found a daily deficit, when the nitrogen of food intake is compared with nitrogen loss in urine and stool Such negative nitrogen balances have been studied by Mosenthal[316] and others Obviously, they indicate a serious disturbance of metabolism Such losses cannot be determined by merely measuring albumin in the urine and estimating hematuria, the information is obtained from studies of metabolism which determine nitrogen intake and output It is worthy of note that there may be a daily nitrogen loss, when at the same time figures for non protein nitrogen or urea in the blood are considerably above the normal and that with blood nitrogen little if at all, above normal there may be a positive nitrogen balance in the urine (Mosenthal and Richards[17]) These variations are not easy to explain very probably nitrogen becomes fixed in the tissue and this explains variations met with (Foster[318])

As already referred to sodium chloride excretion may be much decreased in acute Bright s disease In some cases the daily output is almost nil In such cases usually there is water retention causing edema as already mentioned Quantitation shows some decrease of sodium chloride in many of these patients with increase in a few, but as the sodium chloride of the blood has a threshold of excretion as discussed under Normal Renal Function in Part I the relationship is not so simple as with urea which is a non threshold body For both group chlorides and non protein nitrogen the amount in body fluids and tissues rarely is determinable and this introduces an unknown factor in all deductions from data other than that obtained from studies of total metabolism i e measurements of actual total intake and output

Tests of Renal Function and Changes in Composition of Blood Plasma

The urinary constituents just referred to in their changes mark renal function, but in addition there are certain tests of renal function and certain changes in the composition of blood plasma discussed in Part I which may occur during the course of acute Bright's disease In acute Bright's disease such changes occur as illustrated by the cases described a few pages back In general it may be said that tests of function and blood plasma composition show proportionately less departure from normal in acute than in chronic Bright s disease except when

there is marked oliguria and they are of less importance in the clinical study of the patients except in the later months when they may help in determining whether or not the healing process still is continuing. This is due to several things (1) in acute Bright's disease the kidney may be hyperpermeable (2) some of the tests measure the result of decreased renal excretion and require a considerable time interval before change is at all evident this is especially true of non protein nitrogenous substances in the blood on a diet low in protein (3) in the acute period there may be evidence of marked retention of renal excretory products and yet complete restitution of normal function may occur and so tests indicative of very poor renal function may not indicate that prognosis is bad

Phenolsulfonephthalein excretion[141] in acute Bright's disease sometimes is decreased sometimes normal rarely increased. In the early stages there is no close parallelism in many cases between phthalein excretion and other evidences of activity of renal lesion. In some patients as in one already described (Case V) repeated determinations of phthalein will show a good output and then a decline even though other signs indicate an improvement in the condition. Later in such a case the figure will rise gradually to a normal level. An early low figure or more important one persisting at a low level is indicative of severe renal lesion. As with many other tests not the isolated observation but the repeated determinations give the information of value especially if considered in relation to the other known data of the case. In acute stages with hematuria especially if hemolysis of the blood occurs this interferes with carrying out the phthalein test as it gives a confusing color to the urine. If necessary the blood can be centrifugalized out or precipitated out by methyl alcohol. The same difficulty occurs with a concentrated urine of high color not bloody which is encountered frequently in some stages of acute Bright's disease. In both satisfactory approximate determinations may be made by using a urine of similar color passed before the test to make up the standard solution of phthalein instead of using water. It is interesting that with marked disturbances of renal function in respect to water phthalein excretion often is pretty good and there is no increase in blood nitrogen

Blood nitrogen determinations give normal figures at the beginning of acute Bright's disease while a little later they are usually above normal. Figures of 25 to 30 mgm of urea nitrogen per 100 c c of blood are common higher figures occur often but very high figures are unusual and when found suggest unless there has been continued marked oliguria or anuria an acute exacerbation of a previously existing chronic nephritis although of course this is not always the case. Also in the presence of the occasional marked circulatory collapse nitrogen retention can be caused by this. It is to be remembered that with determinations of urea nitrogen the patient's diet in respect to protein influences the figure when the kidney is damaged. Often a restricted diet whether because of nausea or on

account of medical advice may be responsible for the only moderate increase found For normal kidneys diet within any reasonable bounds does not influence blood nitrogen to force it above the normal level of 20 mgm of urea nitrogen per 100 c c of blood but this certainly is not true when renal excretion is hindered in any way This response to diet sometimes becomes a useful measure of renal function

As with phthalein excretion there is no necessary parallelism between blood nitrogen figures and other signs of renal competency 'Phthalein may be normal and blood urea slightly increased or vice versa In other words, renal permeability for a dye stuff may be normal, while nitrogen retention is taking place or vice versa, although usually these two tests give quite comparable results Duration of action is necessary to lead to increases in blood nitrogen, while 'phthalein is a measure more of the process at the given time This explains some discrepancies Then little is known about the disappearance of the nitrogenous substances from the blood into body fluids and tissues and this may be another factor bringing about differences from the expected result However, urea is such a readily diffusible substance that its amount in the blood is regarded as a pretty good index of its amount in the body in general

Severe toxic symptoms or uremia in acute Bright's disease usually are accompanied by increased blood nitrogen and decreased output of phthalein but according to some this is not always the case and there may be uremic convulsions with practically normal figures for both To the author these seem to have been patients with encephalopathy associated with vascular disturbances rather than patients with cerebral disturbances of uremic origin However, there are pathological lesions in the brain considered to be caused by uremia[319] So the probability of uremic convulsions with normal blood nitrogen and 'phthalein excretion remains In other words, that hypothetical toxic substance or substances that cause uremia may be formed or retained when as measured by phthalein excretion or blood nitrogen determinations renal function is quite good This emphasizes the fact that no single test is a sufficient index of renal function With blood urea determinations as with phthalein estimations, it is the trend of repeated tests along with other disturbances in the patient which are useful and not the single test, whatever the test selected When the figure for blood nitrogen is high and continues so we know renal function is poor and the outlook is correspondingly bad High figures however for a short time by no means contraindicate speedy and complete restoration of function as shown by Cases III and V What has been said applies particularly to estimations of total non protein nitrogen and urea nitrogen in the blood Between the two there is no difference in value of the information obtained Urea determinations are technically simpler and so far as we can judge yield all the information that may be gained from determinations of total non protein nitrogen and at times, according to some, the urea de

terminations are of more value since there is a greater proportionate increase in urea than in total non protein nitrogen

Determinations of the forms of non protein nitrogen other than urea and total non protein in the blood contribute little or nothing of practical value in the study of patients with acute Bright s disease With prolonged marked oliguria they increase in amount but their increase has no particular diagnostic or prognostic implications in addition to those given by determinations of non protein or urea nitrogen The same is true of other constituents of the blood

The *urea clearance test* in acute Bright s disease gives important information of the effectiveness of renal function at the time the test is made Periodic repetition of it informs as to the trend towards improvement if such is taking place Single tests are of very little value in prognosis repeated tests give us more information If urea clearance remains low after albumin has decreased and red blood cells and casts are infrequent in the urine this indicates a trend towards chronicity and the longer this lowered urea clearance persists the less the probability of complete healing of the lesion and the poorer the final prognosis

Inulin mannitol and *diodrast clearances* which measure glomerular filtration rate renal plasma flow and maximal rate of tubular excretion at present are not helpful in the clinical study and management of acute Bright s disease These methods however have thrown important light on the lesions in the kidney and their progression as they influence the functional organization of the kidney[220] As would be expected glomerular filtration rate as measured with inulin or mannitol is the most sensitive indicator of renal change early in the course of acute Bright's disease Somewhat later the other clearance tests show depression of function Tubular function as measured by diodrast becomes more depressed as progression towards chronicity takes place and in the later stages undergoes relatively greater impairment than does the glomerular filtration rate In other words at first glomerular lesions cause most of the decrease in renal function in acute Bright s disease while later and in a sense secondarily tubular function decreases

The various *concentration tests* described in Part I are not of much value in the study of acute Bright s disease especially when the urine is concentrated Later on if the kidney has begun to excrete a rather dilute urine inability to concentrate normally as measured by concentration tests is indicative of failure to heal and if this condition persists it points to a progression into a chronic Bright s disease with eventually poor prognosis

Circulatory Changes

In acute Bright s disease the circulatory changes observed clinically are increase in blood pressure rarely a decrease palpable changes in peripheral arteries enlargement of the heart evidences of cardiac decompensation variations in the

account of medical advice, may be responsible for the only moderate increase found For normal kidneys diet within any reasonable bounds does not influence blood nitrogen to force it above the normal level of 20 mgm of urea nitrogen per 100 c c of blood, but this certainly is not true when renal excretion is hindered in any way This response to diet sometimes becomes a useful measure of renal function

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found in acute Bright s disease unless they were present prior to the acute Bright s disease then arteriosclerosis is a coincidental disturbance not part of the acute Bright s disease However not infrequently larger arteries feel full and are not easily compressible Whether this is more than increased tonus is not certain possibly the muscle layer of the artery has hypertrophied This change in the feel of arteries was noted often by some observers in the type of acute nephritis developing among the soldiers in the trenches in World War I This arterial change has been called by Moschowitz and others *pseudo-arteriosclerosis*

The *heart* in acute Bright s disease shows departure from normal size and normal function more frequently than was thought to be the case before the x ray was much used in determining changes in size and other ways of measuring cardiac function were applied Expressing the view of the past twenty five years ago I wrote The heart is unchanged by acute nephritis except in a rare case where it may be slightly enlarged Such an enlargement however is very difficult to be sure of by any means of physical examination It is safe to regard any easily recognized cardiac enlargement any murmurs or any arrhythmia noted in a patient with acute nephritis as a coincident disturbance probably in no wise related to the nephritis The myocarditis described by some as due to acute nephritis I feel very skeptical about It seems to me far more likely that it is a coincident disturbance or a change in heart muscle caused by the same bacterial or toxic agent that has caused the nephritis Even this type of coincident myocarditis must be extremely rare personally I have never seen a case of acute nephritis in which I thought there was present a myocarditis

In contrast to this a summary of some recent studies show that 34 3 per cent of 391 patients with acute Bright s disease gave evidence of cardiac enlargement or cardiac insufficiency with some patients having moderate to even very marked cardiac decompensation (Marcolongo[226] Ellis[227] Master Haffe and Dack[228] Rubin and Rapoport[229] Whitehill Longcope and Williams[230] Murphy[231]) Particularly interesting clinically are those patients few in number it is true who present themselves with severe dyspnea and edema cardiac enlargement tachycardia pulmonary edema a large tender liver and even pleural effusion and ascites all of which have developed in a short period of time without at first any obvious cause Acute Bright s disease may not be suspected in these patients until urine examination shows albumin blood and casts with decrease in amount sometimes marked oliguria even anuria Some observers as LaDue[232] go so far as to consider that the majority of patients with acute Bright s disease of the hemorrhagic type with edema of the legs have some degree of cardiac insufficiency and may be regarded as patients with congestive failure Here obviously it is difficult to determine whether the edema is derived from renal or cardiac insufficiency

X ray study of numerous patients with acute Bright s disease shows an increase in the size of the cardiac silhouette with corresponding decrease in size as the

electrocardiogram and occurrence of arrhythmias The incidence of these changes is very various not always are they proportionate to the severity of the Bright's disease Some believe them to be of very great frequency[3, 1, 330], others disagree with this interpretation of observed changes in acute Bright's disease

Blood pressure is elevated as a rule when there is severe acute Bright's disease but this may not occur Curiously enough, hypertension may be absent sometimes in very severe cases including those progressing quickly to death Hypertension, according to Fishberg[322], is absent more often in children with acute Bright's disease than in adults According to Blackfan[323, 324, 325] blood pressure is elevated to a greater or less extent in all children with acute glomerular nephritis Blood pressure increase usually is moderate but it may be very marked especially in patients with uremia At the same time it can not be said that blood pressure increase parallels decrease in renal function Blood pressure increase may be present at the very onset of the Bright's disease, or it may appear gradually after many other symptoms and changes from normal have appeared Conversely high blood pressure may precede the albuminuria hematuria, edema and other evidences of acute Bright's disease High blood pressure often precedes uremia, and its appearance may be regarded as evidence of impending uremia Often however cases run their course without any rise in blood pressure being noted In 55 cases at the Peter Bent Brigham Hospital blood pressure was normal in 19, these were adults Duration of hypertension is variable, usually it returns toward normal as other evidences of renal disease decrease Rarely it may outlast most of the signs of acute Bright's disease this suggests progression towards chronic Bright's disease In a rare patient with severe cardiac insufficiency hypotension may be found

In the majority of patients with acute Bright's disease the rise in blood pressure is moderate 20 to 30 mm of mercury but in some patients it is great with systolic level 200 mm or higher and diastolic 120 Systolic and diastolic pressure increases generally run parallel, but in an occasional patient only a systolic rise will be found Without uremic manifestations much elevation of systolic and diastolic pressure particularly if persisting suggests a chronic process underlying the acute manifestations a case of chronic Bright's disease with acute exacerbation rather than acute Bright's disease developing in a kidney previously normal In children according to Blackfan and McKhann[325], a rapidly rising blood pressure soon reaching 150 mm of mercury or higher is evidence of increasing cerebral edema, which if not relieved by appropriate therapy, may result fatally with compression of the medullary cone in the foramen magnum causing respiratory failure from injury of the respiratory center With such cerebral edema there are often, but not always the various symptoms considered to be of the nature of uremia

Changes in the *larger arteries* in the sense of definite arteriosclerosis are not

found in acute Bright s disease unless they were present prior to the acute Bright s disease then *arteriosclerosis is a coincidental disturbance not part of the acute* Bright s disease However not infrequently larger arteries feel full and are not easily compressible Whether this is more than increased tonus is not certain possibly the muscle layer of the artery has hypertrophied This change in the feel of arteries was noted often by some observers in the type of acute nephritis developing among the soldiers in the trenches in World War I This arterial change has been called by Moschowitz and others *pseudo-arteriosclerosis*

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X ray study of numerous patients with acute Bright s disease shows an increase in the size of the cardiac silhouette with corresponding decrease in size as the

Bright s disease clears up A few of these patients show increase in size great enough to be made out by palpation and percussion The electrocardiogram may show the changes described in a subsequent paragraph Venous pressure usually is elevated with subsequent return toward normal levels as the renal condition improves Circulation time according to LaDue[337] is not slowed as might be expected

The exact mechanism of the heart changes in acute Bright s disease is not clear In the majority of the patients there is a definite increase in arterial blood pressure at the onset of heart changes and a fall in this toward normal usually preceeds or accompanies return to normal of the heart changes However, this is not always the case and sometimes heart changes occur in the absence of increased arterial pressure or are well marked before that pressure rises[331 333 464] Certainly in some of these patients cardiac failure is much more marked and the elevated blood pressure of far shorter duration than is seen usually with other forms of hypertension notably idiopathic or essential hypertension with developing cardiac insufficiency Increased arterial pressure scarcely seems to be a satisfactory sole or chief causative factor of the cardiac insufficiency, when it occurs in acute Bright s disease In fatal cases on which postmortem studies have been made no changes have been found in the myocardium of sufficient extent or degree to explain satisfactorily the heart condition which was observed during life it is not a case of acute myocarditis in an histological sense This justifies the last sentence of my statement of twenty five years ago already quoted in the opening paragraph of this discussion of the heart in acute Bright's disease

Acute pericarditis is an occasional occurrence in acute Bright's disease When it occurs characteristic changes develop in the electrocardiogram

Fortunately the cardiac abnormalities seen in acute Bright's disease usually disappear as the Bright s disease clears and only in a very few patients is the condition severe enough to be a cause of death Acute Bright's disease does not seem to initiate heart changes that progress in later years, it is not a cause of chronic heart disease

In the *electrocardiogram* changes in the T wave are seen often Sometimes T waves are flattened or inverted sometimes they are large and pointed Left axis deviation may appear Electrocardiographic abnormalities of some sort have been reported in from 20 to 75 per cent of patients according to different reports With additional leads more changes in the electrocardiograms are found[446] There seems no close correlation between these and the degree of heart failure With subsidence of renal lesions electrocardiographic abnormalities largely disappear

Arrhythmias are not characteristic of acute Bright's disease Infrequent in occurrence when they appear probably they are incidental and an accidental accompaniment This statement does not apply to pulsus alternans which may be found in patients with marked cardiac insufficiency

Pulmonary Changes

In a few patients with acute Bright s disease of hemorrhagic type with normal circulation edema of the lungs is present in degree sufficient to cause slight dulness decreased breath sounds and scattered fine rales over the lower part of the lungs especially in the back With cardiac insufficiency these signs become more marked up to extensive acute pulmonary edema with many fine rales and more dulness to percussion The latter patients may have profuse watery bubbly sputum Some develop pleural effusion with its usual physical signs As complications acute bronchitis and focal pneumonia develop in an occasional patient with acute Bright s disease

The Blood

The average case of acute Bright s disease shows no anemia but with hematuria and a toxic condition moderate to fairly marked degrees of secondary anemia may develop Very exceptionally the anemia becomes a very serious factor in the case It is noteworthy however that many individuals with acute Bright s disease show a cutaneous pallor quite out of proportion to any demonstrable decrease in hemoglobin or red cell count Very occasionally this pallor takes on a sallow or lemon yellow cast suggestive of an hemolytic factor and still there is no definite anemia demonstrable by blood count or hemoglobin determination Moderate leucocytosis is almost the rule in the early acute phase of Bright s disease Increase in blood sedimentation rate is the rule so long as activity of the process persists in the kidney

Ocular Changes

Blurring of vision flashes of light or specks before the eyes are quite frequent complaints of patients Transient blindness occurs infrequently but is a most interesting condition It is a central or at least a retrobulbar condition It develops often with great suddenness and it may disappear with equal celerity Ophthalmoscopic examination usually shows normal eye grounds in patients with such an amaurosis or if changes are found they have no causal relation to the blindness Fortunately except in the very severe usually quickly fatal cases the amaurosis of acute Bright s disease clears up completely

Retinitis is rare in acute Bright s disease Small focal hemorrhages are very uncommon White spots are still more infrequent Rarely edema of the optic disc may be observed Of retinal changes in acute Bright s disease Wagener[337] has written as follows In acute glomerulonephritis as ordinarily seen retinal changes are not found Perhaps in most cases mild retinitis develops at the onset

and is characterized by mild hyperemia of the disk, some arteriolar constriction, mild edema of the disk and a few flame shaped hemorrhages in the vicinity of the disk (acute angiospastic retinitis) This retinitis, however may last only a few days and may leave only slight residuals thus the majority of patients with acute nephritis will show normal fundi" Fishberg and Oppenheimer[338] have stated

The small incidence of severe retinal lesions in acute glomerulonephritis is probably correlated with the fact that hypertension, the pathogenic factor underlying the retinal lesions is marked and persistent in only a small part of the cases though present at one time or another in the large majority of instances Slight changes, notably narrowing of the arteries or haziness of the disk are found in a considerable proportion of the cases, particularly if the fundus is examined repeatedly They have no special prognostic significance The same is true of the occasional small hemorrhages that are found in the fundi, they may be present in the absence of notable hypertension and are apparently akin to the purpuric spots in the skin that are not uncommon in acute glomerulonephritis Duke Elder[339] says ' it is generally agreed that in the first attack of acute glomerulonephritis retinopathy does not occur These several authorities with some individual differences of opinion are in general agreement about the infrequence of more than slight retinal changes in acute Bright s disease, views that accord with the experience of this author

Definite white spots and hemorrhage in the retina always suggest a chronic lesion in the kidney In 36 unselected cases of acute Bright s disease examined at the Peter Bent Brigham Hospital white spots were observed in 3, hemorrhage in one and edema of the disc in one 31 of these patients showed no obvious disturbance in the fundus of the eye The changes in the retina even if they are very marked so as to include edema of the disc scattered hemorrhages and white spots even a macular star may and usually do decrease and disappear entirely as the renal lesion heals If retinal changes persist the probability of development into a chronic phase of Bright s disease is enhanced This is true, too if extensive retinal lesions are seen very early in the development of the acute phase which is under observation

Gastrointestinal Symptoms

Loss of appetite is almost the rule especially in the early stage in acute Bright's disease Nausea and vomiting are not infrequent, they are the rule in the uremic phase if it appears Diarrhea occurs but is less frequent than the gastric symptoms Gastrointestinal disturbances occur more often when the acute Bright's disease is in children than when in adults, it is particularly common in children in association with evidences of cerebral edema Of especial interest is the appearance of abdominal pain which can simulate appendicitis less often

cholecystitis so closely as to lead to surgical exploration Such abdominal pain is rare in the hemorrhagic type of acute Bright s disease but not infrequent in the nephrotic type In the latter there may be peritonitis oftenest of pneumococcic etiology

Nervous System Symptoms

Headache is the most frequent symptom referable to the central nervous system in the hemorrhagic type of acute Bright s disease It varies in severity from very slight discomfort to diffuse very severe pain Usually generalized it may have different localizations but there is nothing in type of headache or its distribution that can be said to be characteristic of the headache of acute Bright s disease On the whole severe headache is more frequent in the children with this form of Bright s disease than in the adults With it often goes nausea and vomiting Dulling of the patient s cerebral activities up to coma occurs Muscle twitching and convulsions may develop the latter especially often in children Transient hemiplegic weakness sometimes more localized palsies are encountered Changes in vision already have been described in the section Ocular Changes Apart from the optic nerve disturbance in the other cranial nerves and in the *spinal nerves are infrequent An occasional neuritis is thought by some to be the* result of a preceding or concomitant infection and not caused by the renal disease, it may result from avitaminosis

Any or all of the nervous system disturbances may develop gradually or rapidly appear early or late in the course of the Bright s disease and clear up slowly gradually or abruptly In the majority of the patients recovery is complete and no residual nervous system symptoms are left Their occurrence has very little relation to final prognosis except in the very ill patients in whom they almost always persist In the small percentage of patients with Bright s disease of the acute hemorrhagic type that die severe nervous system symptoms are the *rule*

The mechanism of nervous system symptoms varies In some cerebral edema seems to be a definite cause especially when the symptoms occur in children Here there is no parallelism to the degree of nitrogen retention Nervous system symptoms with evidences of marked renal retention are regarded as being uremic the probable mechanism of this has been discussed under appropriate heading in Part I In some of these patients the hypertension probably is a causative factor some students of Bright s disease believe that hypertensive encephalopathy is present frequently to cause the symptoms under discussion Their temporary or somewhat longer duration and their frequently speedy disappearance *without residuals do not accord well with the presence of organic lesions* in the vasculature and parenchyma of the central nervous system i e with hyper

tensive encephalopathy, but accord better with a toxic mechanism or cerebral edema as their cause

Other Symptoms

Fever is the rule in this form of acute Bright s disease, but usually it is of moderate degree lasting a few days to two weeks, rarely longer In an occasional case fever is a prominent feature with temperatures of 102° F or higher There is no characteristic pattern to the fever in an occasional patient chills may occur In some patients the infectious process that has caused the Bright s disease in part at least is the cause of the fever but for most of these patients the fever can be regarded as an integral part of the Bright s disease A rare patient is so dominantly febrile that there is some danger of overlooking its cause, namely, the acute Bright s disease and to regard the patient as having some sort of infectious disease with the changes in the urine a result of the infectious disease without there being a lesion in the kidney that could be termed a definite nephritis

The *skin* usually shows pallor not entirely due to anemia and not in association with its edema Edema however when present contributes to the pallor Some of the patients show a pale yellowish tint to the pallor which is not jaundice In some patients purpuric spots appear and/or a positive tourniquet test In these patients as a rule there is no platelet deficiency to explain the bleeding tendency Some patients may have *epistaxes*

Lumbar pain is present in some patients usually mild sometimes quite severe, sometimes radiating to the genitalia and into the groin and thigh regions With the pain there may be costovertebral angle tenderness This pain has led to the picture of the patient slightly stooped forward with one or both hands pressed into his flank region which in the past so frequently was seen in advertisements of patent medicines

Clinical Course

The clinical course of acute hemorrhagic Bright s disease may be short a few days to two weeks with an occasional very severe case dying while others recovered More often the disease lasts several to many weeks with many of these, even those of long duration eventually recovering while others of them die Many patients get over all of their symptoms but are left with a urine continuously showing albumin casts and sometimes red blood cells In some orthostatic albuminuria is a residual change The majority of those with persistent, continuous non orthostatic albuminuria sooner or later progress into the clinical picture of chronic Bright s disease Some of the patients with acute hemorrhagic Bright s disease progress without intermission through a subacute

stage of lessened disturbance into the symptoms and signs of a chronic Bright s disease which then may continue a steady rather rapid downward progress or remain for a long time with very slowly increasing symptoms and signs When the chronic stage is reached recovery does not take place although fairly good health is possible over even long periods of time Just what the clinical course will be seems to have very little relation to the clinical characteristics and severity of illness in the early stages of the condition The discussion of prognosis in the next section has a bearing on the clinical course of acute hemorrhagic Bright s disease

Prognosis

Prognosis both immediate and final in the hemorrhagic type of acute Bright s disease here under discussion is good Relatively few patients die in the acute stage and many recover so completely as to run their expected duration of life without the handicap of any renal insufficiency consequent to their period of acute Bright s disease There is considerable evidence that an attack of acute Bright s disease of this kind produces a certain immunity against the recurrence of acute Bright s disease even if there is a recurrence of the infection that was the etiological factor in the acute renal disease of the individual It is not very uncommon to see a patient who has recovered from acute Bright s disease have one or several recurrences of the acute sore throat or other respiratory tract infection etc which preceded his acute Bright s disease without any accompanying or following recurrence of albuminuria hematuria or other evidence of acute Bright s disease In some patients healing does not take place and gradually or after a latent period of normal health evidences of chronic Bright s disease appear In those patients in whom the renal lesion has not healed in contrast to what has been stated for healed cases recurrent infections often bring return of evidences of active acute renal process in these the element of an acquired immunity may even have been replaced by one of increased renal susceptibility In some patients advance in the extent of the pathological process in their kidneys takes place in a step wise progression following repeated acute exacerbations each following some acute infectious process

Extensive clinical studies of the hemorrhagic type of acute Bright s disease which include follow up over a period of years with final postmortem appearance of the kidneys do not seem available as a basis for stating with approximate statistical accuracy immediate and final prognoses Even were there such it is likely that they would give a prognosis not so good as actually occurs because in all probability they would not include the milder cases which do not reach the hospital and those and such do occur which are so mild as to escape diagnosis

For immediate prognosis in acute Bright s disease we have such statements

as a mortality of less than 5 per cent (Loeb), 3 1 per cent (Lichtwitz), 9 4 per cent in 722 children (Lyttle) for acute Bright's disease following scarlet fever 5 per cent (Trask), 6 per cent (Barasch) and for trench kidney o 8 per cent in 500 cases (Maclean) 2 3 per cent in 300 cases (Keith and Thomson), 3 per cent in 254 cases (Toeniessen) At the Peter Bent Brigham Hospital in patients over 1- years of age (children are not admitted) there have been from its opening in 1913 to the end of 1929 218 patients with acute Bright's disease of which 4 1 per cent died in the acute phase At the Beth Israel Hospital in Boston of 51 cases of acute Bright s disease studied by Derow[347] 2 or 3 92 per cent died in the acute phase Ramberg[483] in a ten year period observed 175 patients with acute nephritis Of these 10 died in the hospital and 4 after discharge a mortality of 8 per cent These several reports show a very considerable variation in mortality which after all probably is not surprising in view of the relatively small number of cases in each report and the great variation in severity that is seen in successive patients with acute nephritis

Ultimate prognosis in cases of acute Bright's disease of the hemorrhagic type not dying from the acute phase, i e the probability of the subsequent development of chronic Bright s disease is reasonably good but how good in a statistical sense is not certain owing to paucity of follow up studies from onset to their death from any cause According to Fishberg the proportion of cases of post scarlatinal glomerulonephritis that terminates in chronic renal disease is very small' He quotes several studies (Caiger Hansborg and Rosenfeld and Rechtenstamm) and says, from these figures it is seen that one may assure parents of children who have recovered from post scarlatinal glomerulonephritis, that the chances of chronic renal disease are extremely small ' As to scarlet fever Trask says in discussing the complication of nephritis that chronic nephritis is rare , and Hansborg[334] found only 2 cases of persistent albuminuria out of 284 patients 1 to 10 years after they were discharged from the hospital where they had been treated for post scarlatinal nephritis Fishberg considers that the incidence of chronic renal disease is higher after acute glomerulonephritis following tonsillitis and other infections" than after scarlet fever and that ' in adults the frequency of development of a chronic process seems to be decidedly greater than in child hood Further he says my experience in adults with definite glomerulonephritis has been that less than one half the patients recover completely" Among 148 cases followed up by Ramsberg[483] 108 were well, 29 were not cured and recurrent nephritis had appeared in 11 She found the percentage of recovery highest in the younger age groups Curiously she found that in the majority of those not cured the nephritis had begun insidiously without acute infectious disease while the acute initial stage usually had been characteristic in those in whom reexamination showed that they were well Hayman and Martin[335] in a group of 495 patients collected from seven reports found that cure

was reported in a range of 42 5 to 85 4 per cent a latent phase in 17 3 to 32 per cent and progression into chronicity in 3 8 to 41 7 per cent

Derow[347] has followed up a group of 51 patients with these results 2 died during the acute phase 42 recovered as determined by the absence of persisting albuminuria and hematuria or the presence of albuminuria of demonstrated orthostatic nature and 7 progressed into what he terms chronic glomerulonephritis with the presence of continued albuminuria as the minimal evidence of chronicity Of the 2 fatal cases one died 6 weeks the other 5 months after the onset both with persistent generalized edema hematuria elevated blood pressure Of those developing chronic Bright s disease one died 3 years and 10 months after onset with evidences of renal insufficiency and congestive cardiac failure the others were still in fair health 2 years 2 years and 2 months 5 years 6½ years 7½ years and 8 years after onset Of the 42 cases of recovery recovery was demonstrated in 2 at the end of ½ month in 15 at end of 1 month in 3 at end of 1½ months in 7 at end of 2 months in 3 at end of 3 months, 2 at the end of 4 months 3 at the end of 6 months and 1 each at the end of 7 9 12 and 24 months in 3 cases a definite time of recovery could not be assigned because of a long period of no observations between discharge from hospital and first finding of evidence that recovery had occurred It is of especial interest in these figures that of 42 patients 27 were well within 2 months after onset and 8 more within 6 months following onset while 1 took 2 years before recovery was demonstrated by albuminuria becoming of orthostatic nature

The wide range in percentage of fatality of recovery and of progression into chronicity points to a wide range of variables that are concerned in determining prognosis as an accurate statistical pronouncement Certainly different groups of patients vary in the severity of their Bright s disease Another important variable lies in variation in diagnostic criteria for mild cases If slight and transitory albuminuria during the course of or immediately following an infection or infectious disease is regarded as true Bright s disease obviously prognosis is vastly better for such inclusions in the group of cases reported as acute Bright s disease there seem to be no generally accepted criteria of diagnosis for such patients as to when and when not to call them acute Bright s disease Also criteria of cure versus chronicity appear to vary and bring into the statistics of different reporters another variable Failure to recognize post nephritic orthostatic albuminuria *discussed on a subsequent page easily may be an important source* of error in determining recovery versus progression into chronicity

Prognosis immediate or ultimate, can not be predicted with much satisfaction on the basis of study of the patient during the acute phase Severely ill patients often recover completely while a mildly ill patient may be the one to continue into a progressing chronic Bright s disease Many students of the disease have commented that the patients with every evidence of very active renal disease often

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A high level of non protein and urea nitrogen in the blood often is seen in patients who recover completely but a continued increase above normal on a diet restricted in protein or repeated rises above normal when the protein in the food is increased points to a developing chronic Bright s disease The same is true of a continued lowered phthalein excretion

From all of this it is obvious that it is very difficult to determine prognosis in any satisfactory way during the earlier acute stages of acute nephritis Whatever the earlier condition recovery is possible recovery may take place in a few weeks often four to six or recovery may be delayed for several months up to one year or even two and then be complete However even with no symptoms and no abnormal signs in an apparently recovered patient whose urine shows no albumin no casts and no blood cells there is the possibility that instead of complete recovery there has developed a *latent phase* of lesion which after a number of years will show evidences of progression into chronic Bright s disease Such latency probably is infrequent as a sequence to recovered acute Bright s disease but that it may occur has been shown by the studies of Addis The method of using Addis counts of casts and red blood cells in concentrated urine specimens has seemed useful in detecting the existence of such latency but the author has had no personal experience with the use of this method in apparently recovered cases of acute Bright s disease

Diagnosis

There is rarely any difficulty in recognizing an acute Bright s disease of the hemorrhagic type from its symptoms and urine changes in particular the presence of blood casts and albumin in considerable amount in the urine Sometimes it is difficult to tell whether the condition is an acute exacerbation of chronic Bright s disease Persisting high blood pressure especially when associated with cardiac hypertrophy is suggestive of an underlying chronic disturbance Extensive retinal changes suggest chronic disturbance Markedly decreased or even moderately decreased renal function when the decrease is out of proportion to the other disturbances always is suggestive that chronic Bright s disease has preceded the present acute attack History of previous symptoms particularly nocturia sometimes helps in the differentiation However there are cases in which time alone will distinguish between an acute Bright s disease and an acute exacerbation of a chronic lesion in the kidney Restoration to normal function indicates the absence of antecedent chronic Bright s disease It is not possible by urine analysis to distinguish between simple acute Bright s disease and an acute exacerbation of chronic Bright s disease

Chronic passive congestion and renal infarction may cause a urine picture almost identical with that of acute Bright s disease Evidences of circulatory

are the ones to clear up promptly and completely and that the Bright s disease following infection with severe manifestations is not necessarily very severe Certainly that has been my experience Severity of the acute attack is no satisfactory criterion of progression into a chronic form of Bright's disease If chronic Bright's disease with a glomerular type of lesion in the kidney is regularly a sequence of acute Bright s disease with glomerular type of renal lesion, then very often the acute phase of the disease has been so mild as to pass unnoticed, for only a few of such chronic cases give a history in any way suggesting preceding acute Bright s disease, a fact which emphasizes further a lack of relationship of ultimate prognosis to severity of acute attack Furthermore the patient with only very mild manifestations may never completely recover to normal renal function Complete anuria for more than a very few days usually portends death in the acute phase In similar fashion extreme, continuing oliguria is a danger signal Uremic symptoms in acute Bright s disease do not have the evil prognosis that they do in chronic Bright s disease Numerous patients with acute Bright s disease have definite uremia and then promptly and completely recover Sometimes a day with numerous convulsions is followed the next day by marked improvement as if a crisis of some sort had taken place but with continued repetition of convulsions the disease is apt to terminate fatally Renal function as measured in various ways may be very poor and yet recovery takes place However repeated tests indicative of continued poor renal function suggest that the renal lesion will not clear and the same is true of continued hypertension A long persistence of hematuria and albuminuria does not preclude ultimate recovery, after one year or even two they may disappear while sometimes a life long persistence of albumin casts and even a few red blood cells may be compatible with good health

A condition of orthostatic albuminuria may persist over long periods of time possibly remain permanently following acute Bright s disease with the patient apparently in normal good health Derow s[347 349] studies of this relationship are of great importance Among 4 recovered cases he found 12 with orthostatic albuminuria but without evidence of chronic Bright s disease These patients he continued to follow and demonstrated the orthostatic nature of the albuminuria in each patient at 3 months 6 months 7 months 8 months 2 years and 7 months 2 years and 8 months 4 years 4 years 10 years and 6 months 10 years and 8 months, 11 years and 1 month and 11 years and 7 months after the onset of their acute Bright s disease If it develops it appears from these studies that orthostatic albuminuria will persist Seven of these patients were 16 years old or younger at time of onset of Bright s disease while 1 each was 30 37, 49, 57 and 59 years old respectively at time of onset showing that age at onset is not a determining factor in their orthostatic albuminuria notwithstanding that the usual form of orthostatic albuminuria occurs in youths to persist for only a few years

PROPHYLAXIS

The most effective prophylaxis consists in the prevention so far as is possible of infections and infectious diseases particularly those of bacterial and especially streptococcic etiology In prevention of such infectious processes it would seem that the prophylactic use of a sulfonamide such as sulfadiazine may play a useful part where otherwise susceptible individuals are gathered together Observations in the army and in civil life indicate that this practice has been effective in decreasing the incidence of respiratory tract infections scarlet fever and rheumatic fever If any infection or infectious disease of possible etiological relationship to Bright s disease does develop its prompt and thorough treatment with a sulfonamide penicillin antitoxin or other appropriate measures should decrease the incidence of the development of acute Bright s disease Whether because of more effective treatment of scarlet fever or because of some unexplained decrease in its virulence and in the occurrence of complications recent years have shown a much decreased occurrence of postscarlatinal Bright s disease Fortunately the diseases of virus etiology play a negligible direct etiological rôle in Bright s disease When Bright s disease appears as a complication or sequel of a virus disease very possibly a secondary bacterial infection is responsible, if this is treated promptly with a *sulfonamide or penicillin as it should be it is probable that there would* be no subsequent acute Bright s disease

TREATMENT

Bed Rest —The most important item in the treatment of acute Bright s disease of the hemorrhagic type is bed rest Even with recent revolts against too strict and too prolonged bed rest there still are no reasons against and every reason for imposing continued bed rest on these patients modified only to the extent of permitting use of a bed side commode for patients experiencing difficulty in urination or defecation in the prone position These patients should not have marked or continued drug sedation

How long should such a patient continue bed rest? All of these patients should be kept in bed for a minimum of four weeks Then if the urine shows no blood edema has disappeared temperature is normal sedimentation rate has approached normal and there are no signs of cardiac insufficiency the patient may be allowed *to sit up for a short period increased from day to day with later addition of slight* moving about increased to moderate exercise provided no untoward symptoms appear and there is no return of blood to the urine A large amount of albumin in the urine and many granular or cellular casts would have the same significance as red blood cells as also would recurrence of edema or fever For most patients however return to the urine of red blood cells is the most significant evidence for

failure or the favorable results of cardiac treatment remove doubt as to the presence of chronic passive congestion Renal infarction is suggested by abrupt onset of pain in one flank if and when pain occurs, and by associated conditions that make embolism or thrombosis probable The edema of serum disease may resemble acute Bright s disease and here as shown by Longcope and Rackemann[336], renal function may be decreased just as in acute Bright s disease, but there is difference in the urine findings as to red cells and casts The very rare case of acute Bright s disease with edema without albuminuria, which at autopsy shows the pathological changes of acute Bright s disease, remains an almost diagnostic impossibility

Many patients with slight albuminuria and a few casts and red cells may suggest early stages of acute Bright s disease These are mainly patients with an infection or infectious disease particularly streptococcic infections and scarlet fever In these Addis counts show as the rule a period of increase in the albumin, casts and red cells When this is more than moderate, the urine picture is indistinguishable from that of a mild or the early stages of acute Bright s disease Actually with consideration of the patient as a whole, and particularly after a few days of observation usually there is no real difficulty in arriving at a correct diagnosis

Some use the term focal nephritis for these patients with infections and infectious disease who develop albuminuria, cylindruria and slight hematuria in the later days of their illness believing that scattered glomeruli and tubules show the same pathological conditions as are found diffusely scattered in kidneys from acute hemorrhagic Bright s disease and that these rapidly heal It seems to this author that nothing is gained by this assumption with the use of the term, focal nephritis or focal Bright's disease an assumption which has not the proof of post mortem study[135] he prefers not to call this condition actual nephritis or Bright's disease but to speak of it as *renal irritation* or *febrile albuminuria*, a condition which will end when the associated disease ends

Orthostatic albuminuria as discussed in Part I at times may so simulate early or slight acute Bright's disease as to cause some difficulty in diagnosis, continued observation and consideration of the age and habitus of the patient will make quite sure that the condition is not Bright s disease As already stated, it may follow acute Bright s disease

In a rare case of acute hemorrhagic Bright s disease associated with dysuria costovertebral pain and quite marked hematuria the condition so simulates hemorrhagic pyelonephritis pyelitis or cystitis tuberculosis of the kidney renal calculus or even renal neoplasm that cystoscopy and pyelography should be utilized promptly in the diagnostic study of the patient to rule out these latter conditions, some of which may require prompt surgical treatment

juices instead of the milk This obviously is a totally inadequate diet from a nutritional viewpoint and so should be continued for only a few days not more than seven

After this brief, semistarvation period a shift should be made to a diet of increased caloric value with a low content in protein and salt carbohydrate and fat should form the larger proportion of the diet for acute Bright s disease Such a diet can be constructed easily enough by any physician and may vary in constituents within a wide range The idea of such a diet is given by the one which we used at the Peter Bent Brigham Hospital under the name low protein salt poor diet estimated to furnish 2 000 calories and to contain on the average not more than 25 grams of protein and 2 grams of sodium chloride per 24 hours when cooked and served without salt The standard for such a diet is as follows with values calculated from food tables such as are in general use

Low Protein Salt Poor Diet Calories 2 000

Food	Amount	Protein	Fat	Carbohydrate	Calories
Cream	200 c c	4 40 gms	80 00 gms	6 00 gms	761 60
Butter	60 gms	60	51 00		461 40
Bread	90	8 28	1 17	47 79	234 81
Sugar	65			65 00	260 00
Potato	100	2 50	10	20 90	94 50
Orange	50	40	10	5 80	25 70
Oatmeal	150	4 20	75	17 25	92 55
Lima Beans	50	2 00	15	7 30	38 55
Corn	100	2 80	1 20	19 00	98 00
Pineapple (canned)	50	20	35	18 20	76 75
Peaches (canned)	100	0	10	10 80	46 90

To the foods given above are added sufficient water tea coffee or cocoa to bring the 24 hour fluid intake up to the level determined on say 1 200 c c or 1 500 c c per day As tea and coffee are diuretics they should be given in small amount preferably only for breakfast better not at all In place of coffee Sanka or Kaffee hag which contain very little caffein and taste very much like real coffee may be used in case tea or coffee keeps the patient awake Possibly caffein low coffees are not diuretic possibly another reason for their use An actual sample menu furnished at the Hospital under the order for a low protein salt poor diet is the following

need of longer bed rest Just how long each patient remains in bed before a trial of the effect of getting up is made, and how long before a trial period of getting up proves safe to continue following the preceding criteria obviously are very variable, stretching out for some patients to many weeks

The patient s bed should be in an airy room but it should be protected against chilling drafts To chill the body has seemed to aggravate the renal process in many instances For a long time it has been advised that patients with acute Bright s disease should wear light weight flannel sleeping garments Nowadays with modern heating and ventilation this hardly is necessary except for children who are difficult to keep covered up while in bed It is important however that when the patient begins to sit up he be so clothed as not to become at all chilled particularly patients should not sit up with bare feet and lower legs They should always feel comfortable as regards the temperature of the room and the absence of sense of chilled body surfaces they should be placed out of any drafts

There is, however a type of Bright s disease in which blood persists in the urine for weeks and in which there is a normal or almost normal renal function What should be the attitude towards this case? First prolongation of rest in bed is clearly indicated until such time as judgment suggests that the patient is at a standstill or even losing ground in bed possibly shown by losing appetite or poor sleep at night It is better now to try the effect on this patient of getting up for short periods If the blood in the urine does not increase, and there is some im provement apparent in general condition then the plan of modified rest with slowly added physical activities is indicated

If the patient with acute Bright s disease persists in showing poor renal func tion as measured by appropriate tests the period of rest should be prolonged until it seems evident that renal function is to be permanently low Such are usually cases with an actual underlying chronic renal process Anyhow, this type of pa tient should be managed as you would chronic Bright s disease namely, limit his activities to the level allowed by his renal function or to put it another way, allow him to do such things as do not appear to harm him as judged by observing symp toms and signs and by estimating from time to time renal function

Diet — Another principle to follow in the treatment of this type of acute Bright s disease is to secure as much rest of renal function as is compatible with adequate nutrition The milk diet of an earlier day often long continued, is no longer advised When nausea is marked withholding of food for 24 to 48 hours is indicated, while supplying needed fluid by slow intravenous infusion of 5 per cent glucose 1 000 to 1 500 c c per 24 hours and allowing the sucking of cracked ice to moisten mouth and throat Some practice a more prolonged period of starvation Usually nausea soon decreases and then mouth feeding is possible At this stage some prefer to give 800 to 1 000 c c of milk (the average glass holds 200 to 250 c c) with crackers or white bread while others prefer to give fruit

1 cup Tea
8 teasp Cream
5 teasp Sugar

2 slices Pineapple
1 cup Tea
8 teasp Cream
5 teasp Sugar

1 cup Tea
8 teasp Cream
5 teasp Sugar
1 slice Bread 3x4½x½
4 teasp Butter

1 sm Pear
2 h tbsp Macaroni
1 cup Tea
8 teasp Cream
5 teasp Sugar

No 5

1 sm bunch Grapes
3 h tbsp Oatmeal
1 slice Bread 3x4½x½
4 teasp Butter
1 cup Coffee
8 teasp Cream
5 teasp Sugar

1 Potato
1 ear Corn
½ glass Cream
1 slice Bread 3x4½x½
4 teasp Butter
1 sm Baked Apple
1 cup Tea
4 teasp Cream
2 teasp Sugar

2 h tbsp Macaroni
1 sm Tomato
1 slice Bread 3x4½x½
4 teasp Butter
2 slices Pineapple
1 cup Tea
8 teasp Cream
1 teasp Sugar

No 6

½ Orange
3 h tbsp Crm of Wheat
1 slice Toast 3x3x½
4 teasp Butter
1 cup Coffee
¼ glass Cream
5 teasp Sugar

¼ cup Cream Soup
1 av size ear of Corn
1 small Potato
1 slice Bread 3x3x½
4 teasp Butter
Spanish Cream
½ glass Cream
1 teasp Sugar
1 Egg white
½ teasp Gelatin
1 cup Tea
4 teasp Cream
2 teasp Sugar

3 h tbsp String Beans
1 sm Peach
1 slice Bread 3x3x½
4 teasp Butter
1 cup Tea
¼ glass Cream
5 teasp Sugar

No 7

1 bunch Grapes
3 h tbsp Oatmeal
1 slice Toast 3x4½x½
4 teasp Butter
1 cup Coffee
8 teasp Cream
1 teasp Sugar

1 sweet Potato
1 ear Corn
Fruit Salad
½ Orange
½ cup Cherries
1 sm Peach
av portion Lettuce
Mayonnaise
1 cup Tea
2 teasp Cream
10 teasp Sugar
1 slice Bread 3x3x½
4 teasp Butter

2 h tbsp Macaroni
2 h tbsp Squash
4 slices Pineapple
24 Dates
1 cup Tea
10 teasp Sugar
1 slice Bread 3x3x½
4 teasp Butter

No 8

½ Orange
3 h tbsp Oatmeal
1 slice Toast 3x4½x½
4 teasp Butter
1 cup Coffee
8 teasp Cream
5 teasp Sugar

¼ cup Cream Soup
1 Potato
1 med Beet
1 slice Bread 3x4½x½
4 teasp Butter
Custard
½ glass Cream
1 teasp Sugar
1 Egg yolk
1 cup Tea

1 boiled Onion
1 sm Peach
1 cup Tea
1 slice Bread 3x4½x½
4 teasp Butter
8 teasp Cream
5 teasp Sugar

This however still is a diet too restricted for long use As soon as there is evidence of distinct improvement and anyhow except in the very ill patient after a ten-day use of the diet just described the patient with acute Bright s disease should be given a diet containing 75 grams or more of protein generous in calories especially if there is good appetite and so arranged as to contain those foods known to be well supplied with vitamins in other words a normal well mixed diet containing fruit and green vegetables in generous proportions Unless the patient shows definite evidence of vitamin deficiency vitamins beyond those in the diet are not needed so far as available evidence shows patients with acute Bright s disease given supplemental vitamins in considerable amount get on no

Breakfast		*Luncheon*		*Supper*	
Baked apple	50 gms	Potato	100 gms	Sliced tomatoes	100 gms
Shredded wheat	30 gms	Corn	100 gms	Macaroni	100 gms
Bread	30 gms	Bread	30 gms	Bread	30 gms
Coffee	150 c c	Tea	150 c c	Tea	150 c c
Cream	40 c c	Cream	20 c c	Sugar	25 gms
Sugar	25 gms	Sugar	10 gms	Cream	40 c c
		Dessert made		Canned pears	100 gms
		of Pineapple	75 gms	Butter total for	
		and cream	50 c c	day	60 gms

This menu as calculated from food tables, totals 25.6 gms protein, 116.6 gms fat, and 247.7 gms carbohydrate yielding 2,143.5 calories

The following menus arranged for patients at home use home measures and may serve as a further example of low protein diets These diets are to be used in their entirety for any given day They are to be eaten without salt, spices or any sort of condiment

Low Protein Diets

No 1	No 2	No 3	No 4
½ Orange	½ Orange	½ Orange	½ Baked Apple
3 h tbsp Crm of Wheat	3 h tbsp Oatmeal	3 h tbsp Oatmeal	3 h tbsp Oatmeal
1 slice Bread 3x4½x½	1 slice Toast 3x4½x½	1 slice Toast 3x4½x½	1 slice Toast 3x4½x½
4 teasp Butter	4 teasp Butter	4 teasp Butter	4 teasp Butter
1 cup Coffee	1 cup Coffee	1 cup Coffee	1 cup Coffee
8 teasp Cream	8 teasp Cream	8 teasp Cream	8 teasp Cream
5 teasp Sugar	5 teasp Sugar	5 teasp Sugar	5 teasp Sugar
½ cup Cream Soup	½ cup Cream Soup	½ cup Cream Soup	½ cup Cream Soup
1 Potato	1 Potato	1 Potato	1 Potato
3 h tbsp Peas	3 h tbsp Carrots	1 Beet	2 h tbsp Squash
1 slice Bread 3x4½x½	1 slice Bread 3x4½x½	1 slice Bread 3x4½x½	1 slice Bread 3x4½x½
4 teasp Butter	4 teasp Butter	4 teasp Butter	4 teasp Butter
Blanc Mange	Spanish Cream	Blanc Mange	Fruit Salad
⅓ cup Cream	½ cup Cream	¼ glass Cream	¼ Apple
1 teasp Sugar	1 teasp Sugar	1 teasp Sugar	¼ Peach
1 Egg white	1 Egg white	1 Egg white	¼ cup Cherries
1 teasp Cornstarch	⅕ teasp Gelatin	1 teasp Cornstarch	av portion Lettuce Mayonnaise
1 cup Tea	1 cup Tea	4 teasp Cream	1 cup Tea
4 teasp Cream	8 teasp Cream	1 cup Tea	4 teasp Cream
2 teasp Sugar	2 teasp Sugar	2 teasp Sugar	2 teasp Sugar
3 h tbsp Cabbage	2 h tbsp Macaroni	2 h tbsp Macaroni	2 h tbsp Peas
1 slice Bread 3x4½x½	1 sm Tomato	1 med Tomato	1 slice Bread 3x4½x½
4 teasp Butter	1 slice Bread 3x4½x½	3 h teasp Apple Sauce	4 teasp Butter
3 h tbsp Apple Sauce	4 teasp Butter		

his actual thirst A careful history as to amount of water taken normally and observation of the patient s water drinking habit usually will give all the needed data on this point

When edema is excessive much stricter fluid limitations are necessary and *here some discomfort to the patient frequently is unavoidable With all these* patients sucking ice relieves much of the craving for water without supplying any very great amount of fluid to the patient The physician of an earlier day had had these patients chew slippery elm bark, if they found it pleasant

When uremic symptoms develop we increase the activity of paths of elimination as will be seen when the treatment of that phase is discussed and so the fluid supply must be increased by mouth or when nausea and vomiting prevent this by intravenous route So long as there is a response by an increase in urine output the fluid intake needs to be increased and it is to the uremic patients that the largest amounts of fluid are given in the present mode of treating Bright s disease

The principle underlying the restriction of the protein salt and fluid for the patient with severe acute Bright s disease is an attempt to reduce the intake of those *substances (nitrogen compounds including the extractives sodium chloride* and water) which we know accumulate within the body when the kidney is damaged as shown by increase of nitrogenous bodies and of sodium chloride in the blood stream and the development of edema (water retention) The excretion of these substances through the damaged kidney is difficult and presumably their excretion throws added work on the kidney Conversely reduction in the amount to be excreted should decrease renal work the principle of physiological rest which theoretically should give more opportunity for restoration of function and repair of structure It is to be remembered however that water is a necessary factor in the excretion of all solids and a certain amount gives an optimal excretion for each patient Too great restriction of water intake may lead to nitrogenous retention On the other hand we have evidence that increased fluid intake at times decreases urine output including salt and nitrogen, and that increased protein intake increases blood nitrogen and at times seems to lead to nausea or even the development of definite uremia All of this is evidence that with certain levels of fluid and food intake body functions including urine excretion go on with a minimum of strain on the kidney and that such a level is the most advantageous for the kidney damaged by disease There is of course much empiricism in this form of treatment for we do not take into account as a rule to any great extent the fact that one patient may excrete nitrogen normally and water poorly etc we reduce all three in a general way except that it is true that in cases with marked edema we have learned to stress chiefly salt and fluid reduction With our present knowledge the preceding directions as to diet and fluid intake seem to yield clinical results that justify them

better than those without such supplementation of the diet, at least that is the result of my own observation

Undoubtedly in the past patients with Bright's disease suffered from much too great and too prolonged restriction of protein in their diets There is no evidence that protein in itself is harmful to the diseased kidney, and unless the blood shows nitrogen retention, there is no reason for protein restriction beyond the earlier days of the illness Some students of the subject advise generous amounts of protein in the diet as soon as nausea has gone

In regard to limitations of salt in the diet in acute Bright's disease, unless there is persisting edema, this need not be continued beyond the earlier more acute stage of the disease After that time a moderate amount of salt may be added to the food, sufficient to make it palatable During the period of salt restriction, if desired, fruit jellies such as grape jelly, currant jelly, etc or marmalades may be used to make more palatable the otherwise flat tasting foods However, salt eating is largely a question of habit and a patient usually will adapt himself readily and soon without discomfort, to a diet restricted as to salt content, if that is believed to be desirable

Fluid Intake —The amount of fluid in the form of water or as milk coffee, tea fruit juices etc given to the patient with acute Bright s disease should be at neither extreme Unless there is marked edema or nausea there is no occasion for a greatly restricted fluid intake The theory that a large amount of fluid will serve to dilute the urine to prevent its irritating effect or to flush out the kidney is not generally regarded as sound today In the more acute stages a limitation to 1 000 c c of fluid in the 24 hours is indicated with an increase shortly to 1 200 c c to 1 500 c c In setting such limitations it is to be recognized that in hot weather, when the patient sweats the limitation of fluid intake needs to be increased to offset the water lost by sweating If there has been vomiting more fluid is needed to counteract the incidental dehydration Fluid by mouth may increase the vomiting or the patient may decline to take enough fluid Under these circumstances fluid should be given intravenously as 5 per cent glucose in normal saline solution With the vomiting the salt in this is desirable to offset its loss from the body by the vomiting

For the average patient with acute Bright s disease a good rule is that the amount of fluid given should be such as not to prove disagreeable either by reason of being too little to satisfy thirst or by reason of being too much so as to make the patient feel that he is being overfilled with water

It is to be recognized that water drinking for many people is determined more from habit than from body need They accustom themselves to gulp large amounts of water, particularly during meals when far smaller amounts taken slowly would amply satisfy their actual thirst This element needs to be considered in determining whether a given patient is receiving enough fluid to satisfy

Whether *sulfonamides* should be used in acute Bright s disease on the basis of their effectiveness against streptococci remains undecided Many of the sulfonamides at times cause the formation of crystals in the tubules cause hematuria and decrease renal function sometimes to anuria Less often a definite renal lesion results as described elsewhere in this description of Bright s disease under the heading Sulfonamide Kidney Either would be very undesirable in acute Bright s disease and the former would be difficult to detect early with hematuria already present as part of the Bright s disease There are a few reports on the treatment of acute Bright s disease with sulfanilamide Longcope and associates[340] in 1942 have reported favorable results with it in 4 cases Fishberg writes in his book, Hypertension and Nephritis published in 1939 of having used sulfanilamide several times in the treatment of patients with acute glomerulonephritis following streptococcal infections of the throat in whom the throat infection was active In none according to him was there any unequivocal benefit from the drug Crumpler in 1944 reports 17 patients with favorable results from small doses of sulfanilamide given until the patients got well he had no evidences that kidney damage was caused by the drug It would then seem a safe procedure if small doses of sulfanilamide are given and the patients observed carefully to detect early any evidences of toxicity of the drug but more reports are needed before definite advice as to the use of sulfanilamide in acute Bright s disease is justified In contrast to these reports Rapoport and associates[449] report the use of sulfanilamide in 33 children in contrast to its non use in 40 children all diagnosed as having acute glomerulonephritis no differences were observed in the course of the disease in these two groups Sulfadiazine with less frequent toxic reactions would seem preferable to sulfanilamide and should replace it now if a sulfonamide is to be tried

Penicillin may prove more effective it has the advantage of excretion through the kidney without doing any damage to its structures Penicillin so far as the author knows has not been tried extensively One report[438] indicates that penicillin should be used it reports excellent results It would not present the element of renal toxicity for consideration and so could be used without worry on that score It should be fully as effective as sulfonamides against streptococci in etiological relationship to the renal lesion if not more so

Treatment of Special Conditions — *Uremia* — In acute hemorrhagic Bright s disease uremia usually is not a problem for therapeutic measures beyond those already described in this section on treatment particularly the advice given as to fluid intake and intravenous use of glucose and normal saline The former use of sweat baths pilocarpin drastic catharsis and repeated bleedings no longer is advised As we know the condition today they should not be expected to be effective in all probability they did more harm than good anyhow those of us of this old period know they proved of very little help A warm bath with subse-

Diuretics — Diuretic drugs should not be used in this type of Bright s disease even if there is marked oliguria or anuria It is my opinion that they are ineffective and often harmful if given to the patient with acute Bright's disease of the hemorrhagic type, a view based on my own animal experiments and clinical experience

In the presence of marked oliguria or anuria the cautious trial of increased fluids by mouth and intravenous glucose solution, 5 to 10 per cent, is indicated Such fluid is to be regarded as a diuretic The continuance of such fluid intake is to be based on its effect on urine output if it increases the amount of urine, the fluid should be continued or even somewhat increased If there is much vomiting then 5 to 10 per cent glucose in normal salt solution is indicated in amount to correct the dehydration as judged by the appearance of the patient and by hematocrit readings of the blood when apparatus for this is available Vomiting patients are losing both water and salt In some of the dehydrated patients increase in urine will indicate that dehydration is being corrected by the amount of fluid being given and will serve as an indication for its continuance With symptoms of uremia or the presence of nitrogen retention the same use of fluids is advisable, here a fall in blood non protein nitrogen is an additional evidence that the treatment is of some effectiveness

Edema in this type of acute Bright's disease is not a condition indicative of the use of diuretic drugs Diuretic drugs as just stated, are very likely to harm rather than to benefit the function of the kidney of these patients, and, as a rule they will not cause a diuresis Fortunately very few if any, of the patients of this group have sufficient edema to be of serious import, and so edema of itself does not need any special consideration in treatment

Other Drugs — When cardiac decompensation develops in acute Bright's disease, as it sometimes does, and is only moderate in degree the use of *digitalis* by mouth is indicated as in any form of cardiac decompensation When it is severe, often abrupt in appearance prompt intravenous use of *ouabain*, 0 25 mgm, or *strophanthin* 0 5 mgm is indicated repeated as is needed Since the latter group of patients often develop acute pulmonary edema, prompt bleeding with removal of 250 to 500 c c of blood is indicated along with morphine sulfate, 15 mgm given subcutaneously In the patient with acute cardiac decompensation fluid intake should be limited to an amount just enough to check dehydration

Mild *laxatives* of any kind are to be given if the patient s bowels do not move satisfactorily Vigorous catharsis for these patients no longer is advised A *tepid bath* is to be given daily *Sweat baths* no longer are recommended, even for patients in uremia If there is anemia which is infrequent in this variety of acute Bright's disease, *iron* or if the anemia is marked, *transfusion of blood* should be given

of compression from crowding down of the medulla against the walls of the foramen magnum and consequent injury of the respiratory center

Oliguria and Anuria — When present most often watchful waiting i more desirable than active treatment Diuretic drugs should be withheld Fluid should be given as already described in the section on Uremia Warm applications over the kidney regions may be applied at least they have the virtue of doing something that is not harmful Decapsulation of the kidney advised by some has not given results justifying its use with its attendant disturbances at least that is my opinion Methods of peritoneal irrigation[436 437 456] described under treatment of uremia in section on Chronic Non-edematous Bright s Disease should be effective in these patients when anuria continues with rising values for blood urea or non protein nitrogen

Anemia if it occurs should be treated with ferrous sulfate With diet long restricted as formerly was advised anemia was more frequent following acute Bright s disease than at present with the custom of giving these patients a generous diet The actual blood lost in the urine of these patients is not a factor productive of anemia except in the rather rare case with prolonged hematuria Fortunately the toxicity from renal retention which is the chief causative factor of anemia in chronic Bright s disease almost always is too brief in the acute cases to be effective in causing anemia

Infections, when they occur in acute Bright s disease should receive prompt and thorough surgical treatment Tonsillitis so often the initiation etiology usually has subsided under proper treatment before the acute Bright s disease develops and does not require tonsillectomy If it persists even in minor activity the problem comes up as to what to do about it from the point of view of its maintaining a source of streptococci to keep the renal lesion active or to reactivate it The general feeling is that local treatment with the giving of sulfadiazine or penicillin should be carried out and that tonsillectomy be postponed until the activity and severity of the Bright s disease subsides markedly If tonsillectomy is performed even after convalescence has become well established usually there results some reactivation of the renal lesion with reappearance or increase in red blood cells casts and albumin However as a rule this change subsides quickly and so is no contraindication to tonsillectomy Unfortunately it can not be said that tonsillectomy has been of much permanent benefit if carried out under these circumstances What has been said for tonsillitis applies also to infected sinuses Badly infected and carious teeth should be removed less involved teeth should receive early dental care dental extraction should be preceded and followed by sulfadiazine by mouth 1 gm at 8 12 4 and 8 during the day periods

quent wrapping up in blankets makes some patients feel better, others prefer a tepid bath without the blanket wrapping With uremic manifestations, apart *from those indicative of cerebral edema it seems wisest to attempt to bring about* an increase in excretion of urine by a tentative increase in fluid intake by mouth and by intravenous injection of 5 to 10 per cent glucose solution, the latter combined with normal saline when vomiting has been prominent Tentative in the preceding sentence means trying a fluid intake by mouth of 1,000 c c in 12 hours or intravenously of 500 c c of glucose solution given slowly, better continuously but slowly by the drip method, with an eye open for possible evidence of beginning cardiac decompensation or increase in venous pressure, deciding to continue this or to give more fluid only if urine output increases Bleeding of 250 c c of blood may be tried, if there is no severe anemia its effectiveness is doubtful More than the amount of fluid stated in an earlier sentence, up to 2 500 c c may be found to be optimum With dehydration always more fluid is needed than when there are no evidences of dehydration

If there are signs of increased intracranial pressure which is more common in children than adults, magnesium sulfate 15 to 30 gm by mouth, and the slow intravenous administration of 25 c c of 10 per cent solution of the same are indicated repeated if evidences of increased intracranial pressure reappear Some prefer to use hypertonic solutions of sucrose, 200 c c of 50 per cent, to intravenous magnesium sulfate in these patients

When there is much muscle twitching, intravenous calcium therapy as a solution containing 5 to 10 c c of calcium chloride or 10 to 20 c c of calcium gluconate should be tried As its effect, if attained is apt to be temporary, repetition is indicated

Restlessness if disturbing, is to be controlled by sedatives When marked, morphine should be given It is not contraindicated in these patients If not effective paraldehyde by rectum or even intravenously should be tried In many patients, fortunately very rarely in those with acute Bright's disease, restlessness is almost impossible of control

If convulsions develop after such sedation, the patient is to be guarded against injuring himself and given the treatment as outlined in the two preceding paragraphs If very severe, chloroform anesthesia has been advised Additional discussion of treatment of uremia will be found on subsequent pages *in the sections* under Chronic Non-edematous Bright's Disease

Headache should be treated symptomatically if not a feature of uremia, then it should be managed by the methods just given for treating uremia For symptomatic treatment drugs such as acetylsalicylic acid, acetphenetidin aminopyrin, *the barbiturates* chloral hydrate, *caffein codein even morphine* are available Lumbar puncture sometimes will relieve a severe headache but it should not be used if there are evidences of increased intracranial pressure, as there is a danger

under discussion that many of the patients of this same group especially the adults at autopsy show dominantly glomerular lesions of the varieties seen in fatal cases beginning as acute hemorrhagic nephritis and that other patients with diabetes mellitus become diffusely edematous and die showing a striking particular form of glomerular lesion intercapillary glomerulonephritis (Kimmelstiel Wilson lesion) All of this fails to fit into the usage of the term nephrosis for the group of patients now under discussion These observers also are forced to separate the cases into two groups sometimes indistinguishable clinically in their earlier stages one of which they call true or lipoid nephrosis the other the nephrotic type of glomerulonephritis

How to explain the marked albuminuria and edema in this group of patients is the problem on whose solution depends the nomenclature and classification There seems to be considerable agreement that the edema of these patients results chiefly if not completely from hypoproteinemia and that this is caused by the leakage from the blood plasma into the urine of protein Since the larger proportion of the protein leaking into the urine is albumin the more essential causative factor of the edema is hypoalbuminemia The mechanism of this edema has been discussed in considerable detail by myself in Part I and needs here no further comment

There have been differences of opinion among investigators as to the cause of the leakage into the urine of the large amounts of albumin found in patients of this group These investigators may be divided into three groups (1) those who have the belief that some kind of a disturbance of metabolism has taken place which has so changed the composition of plasma protein that a considerable moiety of it differs from that present under normal conditions and acting as do foreign proteins introduced into the circulation are not held back by the filtration membrane of normal glomeruli the term diabetes albuminuricus has been suggested (2) those who believe that there is a lipoid type of tubular degeneration, and that this is the causative lesion of the condition justifying the terms, tubular nephritis lipoid nephrosis (3) those who believe that protein passes in large amount through the glomerular membrane not because of change in composition of the protein but because of change in the glomeruli increasing their permeability and that protein is reabsorbed in decreased amount by the tubules in proportion to any injury that has taken place in their lining cells

To me this last explanation seems the one to fit best with what we know about renal excretion and the disturbances that we have observed in it as well as with what we have learned from the study of the clinical course of disease in these patients and in those with other forms of diffuse renal disease i e Bright s disease This explanation assumes that as in other forms of Bright s disease damage to the glomerulus has taken place and that the damaged glomerulus acting as a filtering membrane no longer holds back molecules of a size too great to pass

ACUTE, SUBACUTE AND CHRONIC EDEMATOUS BRIGHT'S DISEASE (NEPHROTIC TYPE)

(Nephrotic Syndrome of Bright's Disease)

Introduction

Included in the above titles are patients in whom the dominant features are generalized edema and high grade albuminuria, both of which almost always are insidious in onset These patients very usually have in addition hypoproteinemia and hypercholesterolemia In a temporal sense this group may be subdivided into acute, subacute and chronic Since, except for duration they have such similar clinical pictures it has seemed to me better not to deal with them separately as acute, subacute or chronic but to discuss them as a group in which individual patients, otherwise similar, vary in their duration, and for brevity to speak of the group as the nephrotic syndrome of Bright's disease The greater number of these patients in duration are subacute Some of them recover some die in the subacute stage some progress into a chronic condition with or without persisting edema Some degree of these four features, edema, albuminuria hypoproteinemia and hypercholesterolemia occur almost always at some period during the course of chronic Bright's disease with the lesions of chronic glomerulonephritis at autopsy[447]

Terminology

The terminology for patients in this group has been the subject of much discussion and relatively little agreement Although clinicians are very largely in agreement as to the onset of disease the symptomatology, the physical signs, the diagnosis and the prognosis in these patients and hence are discussing the same distinctive group of patients there is very considerable disagreement as to what to name the disease of these patients how to classify them in the clinical nomenclature of diffuse renal disease and how to explain their pathogenesis All of those using the nomenclature in which they favor the term Bright s disease, can agree to speak of them as a form of Bright's disease This usage historically is correct for Richard Bright described such patients in his classic of 1827[1] For those, who prefer to use the term nephritis for the great majority of patients with diffuse progressive renal disease comes the dilemma of inflammation versus degeneration, of the usage of nephrosis for the latter and nephritis for the former These students of the subject need too to recognize that some of the most typical degenerative lesions of the kidney true nephrosis in the nomenclature of the pathologist, such as are caused in man and animal by bichloride of mercury almost never are associated with the extensive edema found in the clinical group here

under discussion that many of the patients of this same group e pecially the adults at autopsy show dominantly glomerular lesions of the varieties seen in fatal cases beginning as acute hemorrhagic nephritis and that other patients with diabetes mellitus become diffusely edematous and die showing a striking particu lar form of glomerular lesion intercapillary glomerulonephritis (Kimmelstiel Wilson lesion) All of this fails to fit into the usage of the term nephrosis for the group of patients now under discussion These observers also are forced to separate the cases into two groups sometimes indistinguishable clinically in their earlier stages one of which they call true or lipoid nephrosis the other the ne phrotic type of glomerulonephritis

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through a normal glomerulus The molecules of the albumins being smaller than the molecules of the globulins pass more easily and in greater amount through a damaged glomerular membrane than do the molecules of the globulins, and hence the leakage of albumins is in larger amount than of globulins Furthermore, according to recent studies which have been cited in Part I, normal renal tubules function in reabsorbing almost all of the protein that passes through undamaged glomeruli If this is accepted, any injury to the tubule cells would decrease protein reabsorption by the tubules and increase the amount reaching the excreted urine, so that if there is in these patients any element of tubular injury this would be an additional causative factor in the albuminuria In brief if these views are accepted then the chief cause of this form of renal disease is an injury to the glomerulus which increases its permeability so that molecules of a size formerly held back now pass through it and in very considerable amount, while an abnormally lessened amount of this is reabsorbed by the tubules which in turn are not normal This is the view that I have come to hold and hence I regard this group merely as a special form of Bright's disease or, if you prefer to use the term nephritis as a special form of nephritis, to be more specific, of glomerular nephritis, in which the most fundamental change from normal lies in that part of the glomerulus concerned in filtration, and in which injury to the tubules which can decrease reabsorption of protein plays some, but a less significant role On the basis of this conception of disease in the group of patients which I have designated acute subacute and chronic edematous Bright's disease (nephrotic type) or the nephrotic syndrome of Bright's disease I will now discuss their etiology pathology and pathogenesis incidence, symptomatology and clinical course diagnosis prognosis and treatment

Etiology

Some of these patients have the same etiological relationship to infections and infectious diseases as do patients with the acute hemorrhagic type of Bright's disease which has been discussed already on previous pages In them streptococci most frequently are causative However in numerous patients of this edematous group onset is insidious and no definite etiology can be assigned for each of them, they have not followed a recognized infection or infectious disease This latter situation is particularly true of that relatively infrequent patient actually very infrequent among adults which presents the special criteria considered as diagnostic of the condition called by many true or lipoid nephrosis in contradistinction to the much more frequently occurring patient considered by the same observers as having the nephrotic syndrome of glomerular nephritis As far as my own observations go, patients with extensive persisting edema can date their illness frequently back to an infection or infectious process when they consider their illness

to have begun at a time when they first began to feel below par and not from the day on which first the presence of edema was noted In other words it seems to me that in the group of patients now under discussion infections and infectious diseases have almost as important an etiological role as in the acute hemorrhagic type of Bright s disease In a few patients of this group syphilis seems to have been the cause[448, 451] with modern methods of therapy of syphilis they give a very striking and satisfactory response which s ems proof of syphilis as their cause

Pathology and Pathogenesis

The kidneys from this group of patients when dying relatively early in their disease are of normal or somewhat larger than normal size smooth with a capsule that strips away easily They are gray or yellowish gray in color on surface and cut surface the latter streaked with areas more yellow in color The cortex is paler than the medulla and sometimes has a greasy feel In a few cases of long duration the size of the kidney has become somewhat smaller than normal and still later the kidneys may be definitely shrunken Blood vessels are not prominent and usually no areas of congestion or hemorrhage are seen In many of these patients the glomeruli show under the microscope only slight departures from normal in that the wall of their capillary loops are thickened and may have an hyaline appearance (Bell[131, 137]) special stains may be needed to demonstrate these changes Not infrequently in these there is slight increase in the number of cells of the glomerular tuft Granular material precipitated albumin very often is seen in the spaces about the glomerular tufts Glomeruli are not increased in size and as a rule there are no changes in the capsules of the glomeruli In some of the cases there are no demonstrable changes at all in the glomeruli The tubules usually contain granular detritus and granular and hyaline casts Cells lining the tubules are swollen or flattened and show varying degrees of degeneration evidenced by poorly stained or pyknotic nuclei and increased granularity or vacuolization of the cytoplasm The latter indicates in part deposition of lipoid material this may be found also in cells in the intertubular connective tissue framework sometimes aggregated into foci of considerable size and also in the cells of the glomeruli Often this lipoid material is doubly refractive when viewed through a Nicol prism Some of the students of the subject consider these deposits of doubly refractive lipoid material as pathognomonic of what they call lipoid nephrosis Sometimes such lipoid droplets some of which are doubly refractive are seen in the urine both in cells and casts and in suspension outside of cells and casts In some cases such lipoid material is very slight in amount or even absent This lipoid is considered to be chiefly cholesterol

In most of the patients of this group especially the adults who live for more than a few months the glomeruli show some or all of the changes described in

patients classed as having acute Bright's disease of the hemorrhagic type or its subacute or chronic form these glomerular lesions need no repetition of description at this point in our discussion

How are the abnormalities just described in kidneys of fatal cases of this group to be interpreted? A considerable group of students of the subject believe that the chief lesion is tubular and that the lipoid is evidence of tubular degeneration They consider the glomeruli to be either normal or to show such insignificant departures from normality as to function normally If there is leakage through the glomerular membrane of protein it is, according to these, because of change in the composition of plasma protein rather than from abnormality in the glomeruli Some consider that the lipoid in the renal cells is a deposition and not the result of cell degeneration they think that it appears because of hyperlipoidemia or hypercholesteremia, which is an accompaniment, and indirectly a result of the hypoproteinemia, and according to them, it has very little, if any, injurious effect on renal tubular function It is, in their view, only an incident and not a very important one in the pathology and pathogenesis of this condition

Another group of students consider that the chief disturbance in these kidneys is a change in the glomerulus allowing of passage through the glomerular membrane of a much increased amount of protein, especially of albumin In many patients they believe that at autopsy there are sufficient changes seen in the glomeruli to justify this view and that in many patients glomerular lesions are sufficiently marked to justify speaking of the kidney lesion as glomerulitis or glomerulonephritis For me the fact that in some of these kidneys, even those from patients who for a long time have shown the nephrosis syndrome, there are very slight or no morphological changes in the glomeruli is no reason for not accepting the view that the important renal lesion in these patients lies in the glomeruli a change which causes abnormal leakage of protein through the glomerular filtration membrane into the tubules For me that there is evidence of such leakage is adequate reason for belief in the presence of an abnormality of the glomerulus a pathological lesion in other words That so often there occur in time definite lesions in the glomeruli justifying such terms as intracapillary proliferative glomerulonephritis acute capsular proliferative glomerulonephritis, subacute glomerulonephritis chronic glomerulonephritis, etc is justification for this view that with leakage of albumin there is a causative, pathological lesion in the glomeruli

All of us, who have carried out experiments in small animals, realize that albuminuria can be made to appear in the urine quickly by slight manipulation of the kidney or by very temporary compression of renal veins, an experiment which probably is duplicated in man by the existence of orthostatic albuminuria Although the glomeruli in such animals have become permeable to protein, the most carefully applied histological technique fails to show morphological evidence of

this increased permeability If we accept the allergenic explanation of the glomerular lesions of acute hemorrhagic Bright s disease in relation to their bacteriological etiology as today do most students of the subject then a similar mechanism can be applied for the glomerular changes of the nephrotic syndrome when there are or are not morphologically demonstrable changes in the glomeruli It is well to remember that a transitory increase in capillary permeability is the basis of our widely used skin test for the allergenic qualities of all sorts of substances

I believe that the pathogenesis of the nephrosis syndrome is as follows First there is an injury to the glomerular membrane possibly of allergenic nature which causes increased permeability for albumin resulting in albuminuria of considerable degree Second, the albuminuria causes hypoalbuminemia which with other changes such as salt retention results in edema Third the observed changes in the tubules are largely secondary including the deposition of lipoids the latter being associated with hyperlipoidemia or hypercholesterolemia resulting from possibly as a compensatory process of the hypoalbuminemia and have a minor role in the pathogenesis of the nephrosis syndrome Fourth often progressive morphological changes such as thickening and hyaline transformation of the walls of the capillaries of the glomeruli and proliferation of cells in the glomeruli with at times their degeneration and reparative fibrosis ensue to cause the essential change of the kidney lesion to what all pathologists would call some form of subacute or chronic glomerulonephritis Fifth as these last changes take place there develops out of the original clinical syndrome of nephrosis the clinical picture of advancing chronic non-edematous Bright s disease which is the end stage in the majority of patients of this group who do not recover Sixth progression in an individual patient may show many variations in the clinical picture and also in the changes observed in the kidney when eventually the patient has died either as the result or independently of his Bright s disease

Incidence

Incidence depends much on the limitations set by different observers by their definition of the term nephrosis or nephrosis syndrome If they diagnose as nephrosis true or lipoid nephrosis nephrosis syndrome only those patients with extensive persistent edema normal blood pressure good renal function as measured by phthalein excretion and blood nitrogen level and a urine containing much albumin a varying number of casts but no or only rare red blood cells these patients are so few in number that in a large clinic of adults they may be seen not at all or only very rarely while in a children s clinic they are more numerous but still infrequent If one allows of the presence in the urine of a moderate number of red blood cells or of some degree of hypertension the number of patients materially increases but still they form the smallest group of patients seen with the

diagnosis of some form of Bright's disease or nephritis, a number somewhat larger, if are included diabetic patients with the nephrosis syndrome of Kimmelstiel and Wilson If there are included patients acutely ill with extensive edema, which recedes or entirely disappears in a few weeks, the incidence is increased very considerably If one included all patients who show edema albuminuria hypoproteinemia and hypercholesteremia without cardiocirculatory insufficiency during the course of chronic Bright s disease, who at autopsy show the lesions of chronic glomerulonephritis the incidence becomes large Bloom and Seegal[147] report an incidence of such in 54 per cent of patients followed through to their death and a postmortem examination Another 20 per cent showed one or more but not all of the changes just enumerated in the quadrad as occurring in the 54 per cent

As to age incidence all of the groups separated in the preceding paragraph except the diabetic group occur most frequently in children and young adults with a decreasing frequency as age advances The diabetics with nephrosis syndrome are found most frequently in the middle age to older group of patients As to sex incidence there is no very definite preponderance of males or females With a condition of such relative infrequency of the typical cases the reported groups are of insufficient size to justify any attempt at accurate statistical percentage data of incidence

Symptomatology and Physical Findings

Edema of the subcutaneous tissues and the accumulation of fluid in the serous cavities are the outstanding clinical features of typical patients with the edematous type of Bright s disease the former appearing early and the latter usually following shortly after the edema of the subcutaneous tissue is marked The urine contains much albumin many casts and decreased sodium chloride, water excretion is much decreased these are the characteristics of the urine Beyond these changes and their effects on body function, it is surprising how little is found in these patients that is abnormal It is the edema and the fluid in serous cavities that cause almost all of the symptoms that appear in these patients

The usual symptomatology and physical findings are well shown by the following illustrative cases

Illustrative Cases

Case VIII —A girl of 15 was admitted to the hospital P B B H Med No 10,325 on Feb 19 1919 and again on May 17 1919 with Med No 11098 During the summer of 1918 she had noted some puffiness around the ankles which disappeared on rest Her tonsils were large and obstructive for this reason they were removed in Nov 1918 In the latter part of Nov she had what was called flu and was in bed for 3 weeks Soon thereafter she noticed puffiness of her legs and arms her eye were so swollen she

could hardly open them in the morning When she came into the hospital on Feb 19 1919 her face was swollen especially about the eyes there was marked edema of ankles and legs some fluid was present in the abdomen Her heart seemed normal and her blood pressure was 140/75 Urine contained a large amount of albumin (large trace) a few hyaline and granular casts a few white blood cells but no red blood cells In the hospital in a few days she had a diuresis and soon lost 8 kilos in weight In about a month however edema recurred while she was up and about but back in bed it soon disappeared Urine continued to show features already noted with specific gravity on concentration test ranging from 1 010 to 1 028 Phthalein excretion ranged between 45% and 74% and blood urea nitrogen from 8 to 14 mgm per 100 c c

Going home on Apr 6 edema soon recurred and persisted she returned to the hospital on May 17 with edema and urine findings as on previous hospital stay In this hospital stay phthalein excretion ranged from 40% to 60% and blood urea nitrogen from 9 to 10 mgm per 100 c c

The patient was not seen until Aug 14 1921 when she came to the Out Door Department She had continued to have edema of lower legs varying in amount but never very much Now her urine showed a slight trace of albumin Her blood pressure was 128/90 Headaches were frequent

In 1922 she was seen once with some swelling of ankles She was having occasional frontal headaches accompanied by nausea and vomiting Fundi of her eyes showed some tortuosity of arteries no A V nicking no hemorrhages no exudate Radial arteries were moderately thickened blood pressure 132/92

In 1923 she reported she was feeling fine with swelling of feet only when tired Now urine showed slight trace of albumin and normal phthalein excretion She was not seen in 1924 and 1925

In 1926 this patient was seen twice Occasionally she had headache sometimes her feet swelled and occasionally her eyes were puffy in the morning Physical examination was negative and blood pressure was 135/82 She was not seen in 1927 1928 and 1929

On Feb 15 1930 she reported that her condition had been uneventful since 1926 but now she had a persistent slight headache Her urine was entirely negative Her phthalein excretion was 75% her blood urea nitrogen was 7 mgm per 100 c c her blood pressure was 115/80 x ray of chest was negative She complained of pruritus vulvae for which she was referred to a skin clinic Since then she has not been seen

Summary Case VIII — In the summer of 1918 signs of Bright s disease commenced In 1919 twice in the hospital she showed extensive edema normal blood pressure urine rich in albumin with a few hyaline and granular casts a few white blood cells no red blood cells Renal function by phthalein excretion and blood urea nitrogen level was normal or slightly depressed Edema continued although decreasing through 1922 (4 years after onset) albuminuria slowly lessened During 4 more years edema appeared occasionally albuminuria was slight renal function was normal Four years later i e 12 years after onset urine was normal phthalein excretion was 75% blood urea nitrogen was 7 mgm per

diagnosis of some form of Bright's disease or nephritis, a number somewhat larger if are included diabetic patients with the nephrosis syndrome of Kimmelstiel and Wilson If there are included patients acutely ill with extensive edema which recedes or entirely disappears in a few weeks, the incidence is increased very considerably If one included all patients, who show edema, albuminuria hypoproteinemia and hypercholesteremia without cardiocirculatory insufficiency during the course of chronic Bright s disease, who at autopsy show the lesions of chronic glomerulonephritis, the incidence becomes large Bloom and Seegal[147] report an incidence of such in 54 per cent of patients followed through to their death and a postmortem examination Another 20 per cent showed one or more but not all of the changes just enumerated in the quadrad as occurring in the 54 per cent

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The usual symptomatology and physical findings are well shown by the following illustrative cases

Illustrati e Cases

Case VIII —A girl of 15 was admitted to the hospital P B B H Med No 10,15 on Feb 19 1919 and again on May 17 1919 with Med No 11098 During the summer of 1918 she had noted some puffiness around the ankles which disappeared on rest Her tonsils were large and obstructive for this reason they were removed in Nov 1918 In the latter part of Nov she had what was called flu and was in bed for 3 weeks Soon thereafter she noticed puffiness of her legs and arms her eye were so swollen she

TABLE III

URINE EXAMINATION CASE IX

Date	4 Hr Amt	Sp Gr	Alb	Cast Hy	Cast Gran	Cast Cell	R B C	W B C
1917								
Sept 1		1 0 2	++	* ++			+	++
Sept 10		1 019	+++	++	++		++	++
Sept 19		1 018	+++	++	++		++	++
Sept 28		1 016	++					
Oct 9	465	1 015	+++	+++	++		++	++
Nov 9	210	1 010	+++	++	++		++	++
Nov 19	584	1 017	++	++	++++		++	++
Nov 30	432	1 015	+++	++	++			++
Dec 10	452	1 016	++	++	++		+++	+++
Dec 21	486	1 016	++	++++	++		+	++++
Dec 31	268	1 017	++	++++	++++		+++	++++
1918								
Jan 11	230	1 022	++	+++	++		+	+++
Jan 21	28	1 018	++	++	++		+	+
Feb	400	1 0 3	++	+++	+++		+	+++
Feb 11	462	1 022	++	++++	+++		+	+++
Feb 21	410	1 018	++	+	+++		+	+++
Feb 8	283	1 019	++	+++	++		+++	++
Mar 11	98	1 0 2	++	+	++		+++	+++
Mar 21	250	1 017	++	++	++		+++	+++
Apr 1	[illegible]8	1 01	++		+++		+	++
Apr 12	23	1 019	++	++	++		+	+++
Apr 2		1 021	++	+++++	++		++++	+++
May 3	163	1 024	++	++	++		+++	++++
May 13	5 2	1 017	+++	++	+			+++
May 4	315	1 018	++	+++			+	+++
June 2	530	1 017	++	++	++		+	+++
June 14	6 8	1 0 2	+++	+++	+++		+	+++
June 24	535	1 0 0	++	++	+		+	++
July 4	544	1 022	+++	+++	+	++	+	+
July 15	[illegible]8	1 0 0	++	+++++	+		+	+++
July 6	571	1 014	+++	+++++	+++	+++		++
Aug 4	1 116	1 018	+++		+			+
Aug 11	1 353	1 015	+++		+		+	+
Aug 6	858	1 018	+++	++	+++			+++
Sept 6	510	1 01[illegible]	+++	++++	+++			+++
Sept 15	693	1 012	++	+	++			+++
Sept 20	181	1 024	++	+++++	++++		+	+++

Sp Gr = Specific Gravity Alb = Albumin Hy = Hyaline Gran = Granular
Cell = Cellular R. B C = Red blood cells W B C = White blood cells

* + = Very slight trace of albumin
++ = Slight trace of albumin
+++ = Much albumin
++++ = Very much albumin

\+ = Rare
++ = Numerous
+++ = Many
++++ = Very many
+++++ Very very many

100 c c blood pressure was 115/80 and she seemed well This appears to be a patient who recovered from the nephrotic type of Bright s disease and was well 12 years after her renal disease had begun

Case IX — A girl of 10 Med No 7166 was admitted to the hospital on Augu t 31 where she remained until her death on October 8 of the following year a period of 13 months and 8 days She had measles when very young and three years ago what seems to have been a catarrhal jaundice Three months ago she was in the Boston City Ho pital for 13 days with mild diphtheria treated with 24 000 units of antitoxin Two weeks following discharge apparently well of her diphtheria she noted a little puffiness about her eyes and one week later she found that her legs were swollen both eyes and legs being more swollen in the morning than later in the day, but she did not feel sick and so kept up until one week later when she noted that her abdomen had swollen then she went to bed where she remained until coming to the hospital some six weeks later this was about two months after her eyes first showed swelling At home about two weeks before coming to the hospital her abdomen was tapped, and four quarts of greenish fluid were removed After the onset of the swelling about her eyes her appet te continued good she noted nothing abnormal about the appearance of her urine and except for the subcutaneous edema and ascites nothing had seemed abnormal

On admission to the hospital physical examination showed a pale pasty expression with marked puffiness of the eyelids edema of the conjunctivae and slight edema else where of the face there was marked edema of the legs of the lower back and of the abdominal wall The abdomen was distended with shifting dullness and fluid wave There was bilateral dullness below the angle of the scapula increasing to flatness The heart appeared of normal size with a soft systolic murmur at the apex. Blood pressure was 165 mm Hg systolic and 95 mm diastolic There were several carious teeth and a few small palpable lymph nodes in the neck on both sides along the border of the sternocleidomastoid muscle Ophthalmoscopic examination showed normal eye grounds Urine throughout her illness contained albumin very many hyaline and some what fewer granular casts and numerous to very many red blood cells and leucocytes the specific gravity averaged about 1 019 the urine never had sufficient red blood cells to color it (see Table III) Basal metabolism varied between minus 35 and minus 41 per cent

During almost the entire period of observation ophthalmoscopic examination showed no abnormality in her eye grounds She did not develop hemorrhage Ten days before she died the optic discs became slightly blurred and a few spots of exudate came in one eye Her general condition changed relatively little her edema varied somewhat in amount from time to time as hown graphically in the charts (Figs 31 to 34) by variations in her weight the edema never disappeared Ascites was a prominent feature requiring frequent tapping as shown in Table IV

September 1917 October November December

Blood Pressure

Systolic Blood Pressure

Diastolic Blood Pressure

Phthalein %

Phthalein

Blood Urea Nitrogen in Milligrams per 100 C.C. of Blood

Nitrogen Output in Urine in Grams

Blood Urea Nitrogen

Nitrogen in Urine

Blood Chlorides

Blood Chloride in Grams per Liter of Blood

Chloride Output in Urine in Grams

Chloride in Urine

Patients Weight

Urine in C. C.

Patients Weight

Urine in C. C.

FIG 31

December 1917 January February March

Blood Pressure

Systolic Blood Pressure

Diastolic Blood Pressure

Phthalein %

Phthalein

Blood Urea Nitrogen in Milligrams per 100 C.C. of Blood

Nitrogen Output in Urine in Grams

Blood Urea Nitrogen

Nitrogen in Urine

Blood Chloride in Grams per Liter of Blood

Chloride Output in Urine in Grams

Blood Chloride

Chloride in Urine

Patients Weight in Kilos

Urine in C. C.

Urine in C. C.

Patients Weight

FIG 32

TABLE IV

Date of Tappings	*C C Removed*	*Cl in Ascites Gm*		*Cl Intake Gm*		*Cl in Urine Gm*	
August 16 *	4 000						
September 1	5 200						
October 1	4 500			58		113 ,8	
October 29	5 700			56		6 54	
November 13	6 175			30		2 09	
December 10	4 805	32		56		3 66	
January 10	5 900	40		53		2 0	
February 4	6 00	41		48		1 7	
March 7	7 200	47		62	547 gm	5 0	
April 8	6 785	43	438 gm	64		5 0	99 95 gm
May 2	7 230	48		48		1 5	
June 20	10 000	69		60		3 0	
July 17	9 050	64		54		11 0	
September 27	8 260	54		72		65 0	
Postmortem	5 500	24					
	96 500	462		661		113 ,8	

Before entrance to hospital amount only approximate

In all the patient s abdomen was tapped 14 times in 14 months and if the fluid found at autopsy is included the total fluid was 96 500 c c in weight, over three times the weight of the patient This fluid always was opalescent resembling a chylous fluid The table (Table IV) also is of very great interest in showing what a large proportion of the salt ingested found its way into the ascitic fluid The second column of figures shows the grams of salt quantitated in the fluid of each tapping the third column shows the ingested salt between tappings calculated approximately from food tables the last column shows the quantitated excretion of salt in the urine During a period in which 547 grams were ingested 99 95 grams were excreted in the urine and 438 grams into the peritoneal fluid

During her stay in the hospital she developed minor infections On January 24 1918 she had a coryza and cough with slight fever in July 1918 she had bronchitis with a fever as high as 102 6° F On October 15 1917 she developed a thrombosis of the saphenous vein and its branches in her left leg On November 15 1917 two carious teeth were extracted These infections did not seem to cause much change in her renal condition

From time to time she had slight toxic manifestations such as nausea and headache The nausea might have been due to the ascitic fluid Definite uremia was absent and, at the end when she was almost anuric she had Cheyne Stokes respiration and continuous nausea Even then except for moderate drowsiness and slight twitching of the facial muscles there were no nervous disturbances of uremic nature her mind remained clear until she died

Renal function is shown in the charts (Figs 31 to 34) Phthalein excretion in two hour periods fluctuated from time to time but from admission August 31 1917 to December 1917 usually was over 35 per cent until April 1918 usually it was over 30 per cent though occasionally falling below 30 per cent until July 15 1918 it averaged about 30 per cent though often it fell somewhat below that level from July 15 to August 15 1918 it fell steadily to 14 per cent and then fluctuated around that level as long as determined

When first observed blood urea nitrogen was 31 mgm (September 4 1917) under a high protein diet it rose to 77 mgm on September 8 1917 under a low protein diet it fell to 25 mgm on October 24 1917 and on January 16 1918 reached 17 0 mgm at about which level it remained until April 17 1918 when it had risen somewhat reaching 28 6 mgm In June 1918 it rose again under increased protein feeding to 41 mgm Under protein restriction it fell steadily reaching 10 7 mgm on July 24 1918 It then fluctuated between 12 and a little over [illegible]0 until September 18 1918 when it was 14 5 mgm From this point it steadily rose to 40 [illegible]8 90 118 and 122 shortly before her death on October 9 1918

Blood chlorides as shown in the charts (Figs 31 to 34) were always elevated and rose on the few occasions when salt excretion in the urine increased This happened with a diet high in protein and low in salt For much of the time sodium chloride in the urine was very small in amount averaging during the first nine months of observation not more than 0 1 gm per day and frequently was too little to be determined Fluid output was consistently low 300 to 400 c c on a fluid intake of 1 000 c c it was most abundant during the periods of increased protein intake

The charts (Figs 31 to 34) show graphically these fluctuations in phthalein and blood urea nitrogen in relation to amount of urine nitrogen and sodium chloride content of the urine blood chloride fluid intake etc

Blood pressure as shown in the charts (Figs 31 to 34) remained quite constant at a fairly high level for a child to increase to a very high level in the last month of life with a terminal drop just before death

The Wassermann reaction in the blood was negative Usually there was a very slight leucocytosis the counts varying between 6 300 and 13 000 and a moderate secondary anemia developed as shown in Table V

TABLE V

BLOOD COUNT CASE IX

	R B C	Hb
August 31 1917		75%
September 11 1917	5 85[illegible] 000	97%
November 1 1917	3 690 000	60%
November 15 1917	4 440 000	80%
November 30 1917	3 [illegible]80 000	80%
December 6 1917	5 024 000	5[illegible]%
December [illegible] 1917	4 656 000	80%

Blood Pressure
150 Sy tolic Blood Pressure
125
100
75 Diastoli Blood Pr ssure
60
Phthalein %
50
40 Phthalein
30
20
Nitrogen Output in U in in Grams
12
10
8
6
4 Blood Urea Nitrogen
2
0 Nitro n in Urine
Chlorid Output in Urin in Grams
1 6
1.4
1 2 Bl d Chloride
1 0
0 8
0 6
0 4
0.2
0 Chl de in Urine
Urine in C C.
1000
750
500 F uid Weight
250
0 U ine in C. C.

33

June July 1918 August September October
29 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 1 3 5

Blood Pressure
225
200
175
150 Systolic Blood Pre ure
125
100
75 Diastolic Bl od Pr ur
60
Phthalein %
50
40
30 Phth lei
20
Nitrogen Output in U in in Grams
12
10 Nitrog n in Uri
8
6
4 Blood U a Nitro en
2
0
1 6
1 4 Blood Chloride
1.2
1 0
0.8
0 6
0 4 C l d U ine
0.2
0
Urine in C C
1000 Urine in C C
750
500 F W ht

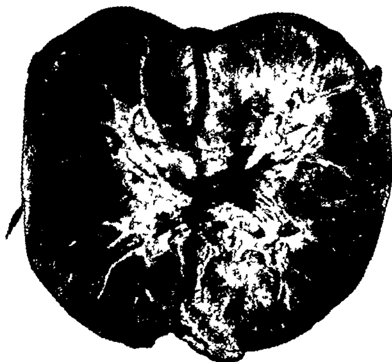


FIG 35 Kidney of Case IX

different portions of tubules are difficult to identify because of the marked atrophy and increase of fibrous tissue The interstitial tissue was almost uniformly infiltrated with lymphoid and plasma cells The majority of the tubules contained hyaline casts The arteries showed very extensive lesions Many showed recent thrombi evidenced by the presence of a hyaline fibrin recticulum in the lumen proliferation of the endothelium and invasion of the walls with polymorphonuclear leucocytes There were a few arteries in the section which showed a concentric thickening of the intima possibly compensatory reaction The arteries showing the thrombi did not contain bacteria demonstrable with eosin methylene blue stain It is possible that these lesions may have been secondary to the glomerular lesions Changes in the pyramid included considerable fibrosis and the presence of tubules containing casts of all sorts

Summary Case IX — Two weeks following mild diphtheria in a child of 10 years puffiness of the eyes was noted a week later her legs were swollen a week later her abdomen was swollen This edema persisted she had few other symptoms hematuria was never noted Physical examination showed extensive edema with ascites and increased blood pressure The urine was albuminous rich in cells and casts and decreased in amount Phthalein excretion though decreased

			R B C	*Hb*
December	27	1917	4 816 000	80%
January	10	1918	4 728 000	80%
January	17	1918	3 776 000	80%
January	31	1918	3,588 000	65%
February	14	1918	3 952 000	75%
February	28	1918	4 344 000	65%
March	14	1918	3 888 000	65%
March	27	1918	4 944 000	75%
April	8	1918	3 912 000	75%
April	25	1918	4 784 000	70%
May	6	1918	4 800 000	70%
May	16	1918	3 568 000	70%
May	23	1918	3 896 000	70%
June	6	1918	2 996 000	65%
June	13,	1918	2 768 000	60%
June	27	1918	3 592 000	75%
July	11,	1918	3 488 000	60%
July	24	1918	4 536 000	75%
August	8	1918	3 208 000	60%
August	15	1918	3 832 000	65%
August	28	1918	4 248 000	65%
September	12	1918	3 904 000	55%
September	19	1918	4 912 000	75%
September	26	1918	3 360 000	75%

The patient died October 9, 1918 and *autopsy* showed no lesion except the renal one the associated edema and moderate heart hypertrophy (weight 225 gm) The kidneys weighed 65 gm and 95 gm respectively Their surface was smooth after stripping the capsule (see Fig 35) They were grayish red in color and mottled with deep red areas from pin point size to 3 to 4 mm in diameter The cortex averaged 6 to 7 mm in thickness The outer two thirds was deep red the inner one third yellowish, the pyramid were red at the periphery and pale centrally *Microscopic examination* (Figs 36 and 37) showed extensive fibrosis of the cortex with numerous sclerosed glomeruli The other glomeruli exhibited all stages of intracapillary and capsular proliferation There were no perfectly normal glomeruli present The commonest lesion was an obliteration of the glomerular capillaries with hyaline material containing numerous large nuclei and therefore probably derived from proliferated endothelium There were many glomeruli which were definitely replaced by fibrous tissue A few glomeruli, which were completely bloodless showed distention of the capillaries with large mononuclear finely vacuolated cells There were numerous polymorphonuclear leucocytes in such glomeruli There were a few glomeruli containing basic staining thrombi of hyaline fibrin with however heavily engorged capillaries as well Such glomeruli invariably showed proliferation of the capsular epithelium In a few instances where the afferent vessel could be found it was thrombosed and filled with hyaline fibrin and surrounded by leucocytes Other glomeruli showed all changes of capsular proliferation up to complete replacement of the proliferated capsular epithelium with fibrous tissue The

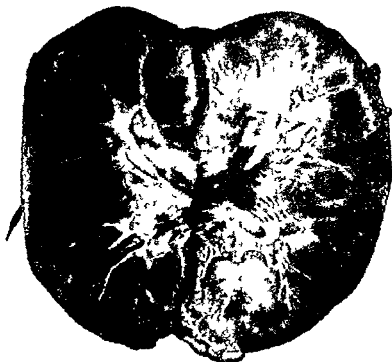


Fig 35 Kidney of Case IX

different portions of tubules are difficult to identify because of the marked atrophy and increase of fibrous tissue The interstitial tissue was almost uniformly infiltrated with lymphoid and plasma cells The majority of the tubules contained hyaline casts The arteries showed very extensive lesion Many showed recent thrombi evidenced by the presence of a hyaline fibrin recticulum in the lumen proliferation of the endothelium and invasion of the walls with polymorphonuclear leucocytes There were a few arteries in the section which showed a concentric thickening of the intima possibly compensatory reaction The arteries showing the thrombi did not contain bacteria demonstrable with eosin methylene blue stain It is possible that these lesions may have been secondary to the glomerular lesions. Changes in the pyramid included considerable fibrosis and the presence of tubules containing casts of all sorts

Summary Case IX — Two weeks following mild diphtheria in a child of 10 years puffiness of the eyes was noted a week later her legs were swollen a week later her abdomen was swollen This edema persisted she had few other symptoms, hematuria was never noted Physical examination showed extensive edema with ascites and increased blood pressure The urine was albuminous rich in cells and casts and decreased in amount Phthalein excretion though decreased

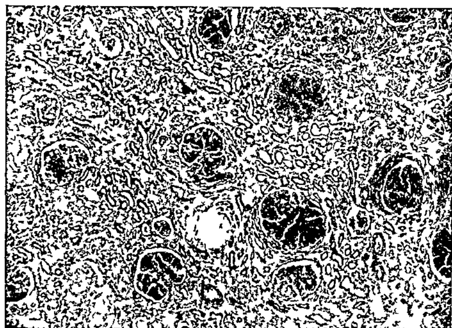


FIG 36 Section of kidney of Case IX under moderate magnification

FIG 37 Section of kidney of case IX under fairly high magnification

remained fairly good until the end blood urea nitrogen was normal or moderately elevated throughout except on high protein feeding and just before death Decreased salt excretion was striking Much of the salt accumulated in the ascitic fluid, this fluid was removed by aspiration 14 times Uremia did not develop Treatment was ineffectual and the patient died approximately *16 months after* the onset of the disease

Case X —A girl of 16 Med No 8832 was in the hospital June 16 to August 3 September 10 to 6 and October 8 until her death on February 22 of the next year She had been well except for measles at 5 and possible whooping cough in early childhood One month ago she had a slight cold and three weeks ago she noticed at the end of the day that her ankles were swollen This increased during a week so as to involve the entire leg and then she noted that her face seemed somewhat puffy so she came into the hospital

Physical examination showed pitting edema of feet ankles lower legs and thighs and slight distention of the abdomen with slight shifting dullness and a definite fluid wave Beyond these findings physical examination was normal and the patient was free of symptoms Her blood pressure was 150 mm Hg systolic and 90 mm diastolic The changes which took place during this stay in the hospital and subsequently appear in the accompanying table (Table VI) Her urine had a specific gravity of 1 022 and showed a considerable amount of albumin numerous casts hyaline granular and cellular a few red blood cells a few more leucocytes and decreased chloride and her phthalein excretion was 45 per cent in two hours Her leucocyte count was 12,400 and hemoglobin 80 per cent Table VII shows the chief findings in her urine throughout her illness Urine volume and chloride output are shown in Table VIII

During the stay in the hospital from June 16 to August 3 her edema disappeared On July 2 she had a severe frontal headache nausea and vomiting On July 24 slight edema of the legs recurred with the patient out of bed After leaving the hospital

TABLE VI

BLOOD PRESSURE CASE X

			Systolic	Diastolic
June	16	1918	1 0	90
July	1	1918	150	100
August	1	1918	150	100
Spetember	10	1918	194	136
October	12	1918	192	128
December	1	1918	190	38
January	6	1919	200	120
February	2	1919	175	20
February	11	1919	192	130
February	17	1919	2 4	124

TABLE VII

URINE EXAMINATIONS AND TESTS OF RENAL FUNCTION CASE X

Date	24 Hr Amt	Sp Gr	Hb	Casts Hy	Casts Gran	Casts Cell	R B C	W B C	Ph	B U N	Bl Cl	Wt
1918				**				**				
June 16	650		++				+	++				70 0
June 18	500+	1 022	+++	++	+++	+++	+	++	45%			
June 30	750	1 022	+++	++	+++	+++	++++	+++++				60 8
July 10	1 017								50%	13 2	5 23	57 6
July 15	651	1 012	+++	+++	++++	++	+	+++				58 0
July 24	500								52%	13 1	5 20	57 2
July 26	742	1 019	+++	++	+++	+	+	++				57 2
Aug 2	620	1 015	+++	+++	+	+		+++	45%			57 0
Sept 15	695	1 017	+++	++++++	++++	+	+++	+++				65 2
Sept 18									15%	14 4	5 52	64 8
Sept 25	600	1 017	+++	++++++	++++	++++	+++	+++	20%	15 8	4 4	63 8
Oct 15	500								+	2, 2	4 35	
Oct 16	550	1 017	+++	+++	+		++	+				
Oct 21	881	1 015	++	++	++++	+++	+	+++				
Oct 23	749								+	20 0	4 45	
Oct 31	1 076	1 015	+++	++	+++	+	+	++	10%	13 2	4 45	61 2
Nov 14	1 475	1 014	++	++	++++	+++	+	++++	15%	21 0	4 8	58 6
Dec 1	1 405	1 023	++	++	++++++	+++	+	++++				57 0
Dec 4	740								7%	23 0	5 29	56 8
Dec 8	1 106	1 016	+++	+	+++++	+++	+	++++++				56 6
Dec 11	424								3%	33 4	5 19	56 2
Dec 18	1 345								4%	24 0	5 00	55 4
Dec 19	955	1 016	+++	++	++++	++	+	++				55 0

TABLE VII (Cont)

Urine Examinations and Tests of Renal Function Case X

Date	24 Hr Amt	Sp Gr	Alb	Casts Hy	Casts Gran	Casts Cell	R B C	W B C	Ph	B U N	Bl Cl	Wt
1919												
Jan 6	700	1 017	+++	++	++	+	+	++++	2 %	5)0	5 33	5(8
Jan 15	650								0	39 0	5 31	53 2
Jan 16	832	1 017	++	++	++++			++				52 6
Jan 22	590								+	32 0	5 41	53 4
Jan 23	895	1 021	++	++	++		+	++				53 2
Jan 29	570								0	25 0	4 53	54 8
Jan 30	710	1 020	+++	+++	++++	+	+	+++++				55 6
Feb 6	635	1 017	++	+++	++++	+	+	++++	0	2 0	5 00	58 2
Feb 12	650								0	20 0	5 00	59 0
Feb 13	520	1 021	+++	+	++++	+	+	++				58 0
Feb 16	458	1 023	+++	++++	++++	+	+	++++				57 2
Feb 17	620	1 023	+++	++++	++++	+	+	++				5/ 0
Feb 19	770											5 6
Feb 20										0 0	5 44	
Feb 22	Died											

Sp Gr = Specific Gravit Alb = Albumin Hy = Hyaline Gran = Granular Cell = Cellular R B C = Red blood cell W B C = White blood cell Ph = Phenolsulphonephthalein excretion in two hours B U N = Blood urea nitrogen in milligram per 100 c c of blood Bl Cl = Blood chloride in grams per liter of blood Wt = Weight in kilos

\+ = Very slight trace of albumin
++ = Slight trace of albumin
+++ = Much albumin
++++ = Very much albumin

\+ = Rare
++ = Numerou
+++ = Many
++++ = Very many
+++++ = Very very many

TABLE VIII

Chloride of Urine Case X

Date	*Average Daily Vol. of Urine*	*Average Daily Output of Chloride*	*Average Daily Intake of Chloride (Only Approximate)*
1918			
June (¹)	957 c c	3.38 gms	1.1 gms for 4 days on milk diet Then 2 gms
July	740	1.70	2
August	780	0.67	2
September	793	1.53	2
October	840	1.09	2**
November	1,064	1.30	2
December	1,053	1.02	2*
1919			
January	1,031	1.97	2
February	697	1.26	2

(¹) Calculated from food table

** October 12 to 15 no food too sick

*December 5 to 12 and 20 to 31 Epstein Diet with 2.5 gms NaCl

August 3 she felt well for a week but remained at home Then she noted a return of edema of her ankles followed in a few days by nausea and vomiting On reduced diet in bed she got much better again On September 7 her face was swollen in the morning and she was nauseated and vomited Two days later she noticed blurring of her vision Her weight increased 4.4 kilos in these 10 days She was readmitted to the hospital on September 10 Although vision had been blurred ophthalmoscopic examination was negative except for a possible slight edema of the left optic nerve head The abdomen contained somewhat more fluid than at the previous admission and there was about the same amount of edema of the legs The tonsils showed some evidence of recent inflammation The second day in the hospital edema of the face was so marked that the patient could barely open her eyes Gradually she improved, although her eyes were puffy each morning She was discharged September 26 as the wards were filling up with influenza patients

After leaving the hospital on September 26 the patient lay down most of the day at home Against advice she drank very large amounts of fluid in the form of water, orangeade tea and cocoa The rest of her diet consisted of fruits vegetables and bran with meat very rarely She did not eat salt free bread However she put no extra salt on her vegetables or other food She continued to feel tired About October 1 she again began to feel nauseated in the morning and would vomit her breakfast The nausea would wear off during the day October 7 her head began to ache It ached very severely particularly over the frontal region She described it as a feeling as if

something heavy were pressing on the head The headache usually became worse in the afternoon but was present all the time October 11 it became extremely severe worse than ever before She took a cup of cocoa on the evening of October 11 and vomited it she remembered nothing more until two days later when she found herself in the hospital For three or four days before admi ion her vision had been somewhat blurred on waking up in the morning This cleared up during the day The day before readmission the patient went into coma On the day of admis ion October 12 she had three generalized convulsion

On October 12 1918 the patient was admitted in coma from which she could be aroused only very slightly by extreme pinching or pricking with a needle *Ophthalmoscopic examination* now showed in the right eye an optic disc with edges distinctly blurred and the retina edematous The vessels were tortuous To the outer side of the disc there was a small patch of shiny white exudate There were a few pin point hemorrhages In the left eye the edge of the optic disc were completely obscured There were many areas of shiny white exudate The retina was edematous The vessels were tortuous There were numerous areas of pin point hemorrhage *Lungs* — Below the angle of the scapulae in both backs there was some dullne more on the left than on the right The breath sounds however came through although they were moderately diminished in character At both bases behind there were rather numerous moist rales The lungs otherwise were clear *Abdomen* was well developed symmetrical No pulsations tenderness masse or spasm No herniae No shifting dullness The abdominal reflexes were present *Liver* was not enlarged edge not felt *Legs* — There was moderate pitting edema of the legs *Heart* — The heart was slightly larger than on previous admission the left border being 12 cm from the mid ternal line Physical examination otherwise was at the previous admis ion

Soon after arriving at the hospital on October 12 the patient had three typical convulsions lasting a few minute The patient had rare lucid moments during her first evening in the ho pital The next morning she wa feeling quite well The following day she was sitting up in bed and said he was feeling finely The edema decreased but did not disappear entirely After a short time it began again to increase and from time to time would vary in amount Occasionally there were nausea and vomiting Early in February 1919 her edema became more marked she had more gastric disturbance and seemed to be in generally poorer condition On February 13 she developed a respiratory infection with a final bronchopneumonia and she grew worse as far as her renal condition and attendant symptoms were concerned until she died February 22 1919

Autopsy — A limited autopsy showed the following in the kidneys Each kidney weighed 175 grams and appeared large They were very pale in color rather soft and more or less succulent in consistency The cortical surfaces were generally smooth except for a few particles carried away with the capsules on stripping these off The cortex measured on the average about 10 mm in depth It was pale yellow with a grayish tinge save for the deeper 2 or 3 mm which were of a brighter yello color and sharply differentiated from the medulla The radiate structure of the cortex wa absent upon the uniform ground of the cut urface of the cortex th re a a v ry fine sanding seen only by reflected light th was due to the glom ruli which c uld

be seen as extremely small and colorless glistening spots standing a minute fraction of a millimeter above the cut surface The pyramids, normal in size, were purplish red with very marked striation centering toward the apices On exposure to the air the purplish hue rapidly turned into a bright red The vessels in the renal substance were not visible The pelves were normal The renal arteries were dissected in situ after opening of the aorta They were approximately of equal length, and their diameters were from 5 to 6 mm The walls of the arteries were soft, although thickened, especially in their initial parts where upon a length of 1 5 cm there were large, soft confluent yellow patches The remaining portions showed a typical tracheal appearance but the folds were at equal intervals two or three succeeding at short intervals of about 1 mm and formed groups leaving between them about 7 or 8 mm of approximately normal wall Sections of kidney showed changes which were most marked in the glomeruli These showed various changes from hyalinization and complete obliteration to thickening of the capsule or obliteration of the intercapsular space by fibrous tissue The greater number of the glomeruli were moderately swollen and the glomerular tufts had a lobed appearance this swelling appeared to be due to proliferation of the endothelial cells There was a moderate diffuse increase of fibrous tissue The tubules in the medulla were much distended and filled with hyaline and granular casts The vessels were not thickened or atheromatous

Summary Case X — A girl of 16 years began to have swelling of the legs There was no antecedent infection except a slight cold As the swelling persisted she came to the hospital It was found that besides edema of the legs there was some fluid in the abdominal cavity The edema disappeared to return later Three months later her face was swollen, she had nausea and vomited Her vision was blurred Fluid was present in her abdomen A month later she had three convulsions and became comatose These symptoms cleared up in a few days Four months later edema was very marked, and she developed a terminal respiratory infection She died nine months after the onset of her illness From the beginning she had increased systolic blood pressure (150 mm) which gradually rose (224 mm) as time went on as shown in the tablé, Table VI There was moderate secondary anemia The urine was decreased in amount rather concentrated contained much albumin and many casts and white blood cells, fewer red blood cells (see Table VII) There was no hematuria in a gross way Urine chloride was decreased Table VIII shows these features of urine 'Phthalein steadily fell from 45 per cent to zero The blood urea nitrogen in the beginning ranged between 13 and 15 mgm gradually increased to 25 to 30 mgm , and a few days before death reached 70 mgm At death the kidneys were large, and glomerular lesions were very prominent

Case XI — A boy of 17 was admitted for 1 week to the Beth Israel Hospital unit history No 18029 on Apr 17 1933 Until 5 months ago i e in December 1932 he had been well except for chronic eczema of the hand Then his legs swelled and in varying degree with varying localization as to upper or lower legs and extending to

the sacrum but without involving the feet this continued Soon swelling of his lower eyelids was noted and continued Except for this edema there had been no other disturbance and there had been no symptoms the patient had kept up and about except for 1 week when edema was most marked At no time had the patient had any respiratory tract infection or any infectious disease The occurrence of smoky or bloody urine never had been observed

Physical Examination Apr 17 1933 —A tall thin boy poorly nourished and pale showed definite puffiness of the eye lids and pitting edema of the sacrum but no edema elsewhere The throat including the tonsils was normal as were heart lungs and abdomen Blood pressure was 104 mm Hg systolic and 75 diastolic Ophthalmoscopic examination showed no abnormality Urine had a specific gravity of 1 035 alkaline reaction a large amount of albumin and no red cell white cell or casts During his hospital stay specific gravity of the urine ranged from 1 035 to 1 018 with a daily amount of 1 350 to 1 500 c c The urine showed in this period no red blood cells but an occasional white cell and cast Phthalein excretion was 55 percent Non protein nitrogen ranged from 24 to 32 mgm per 100 c c plasma protein was 4 53 4 3 and 4 37 gm with albumin 1 53 1 54 and 1 81 and globulin 3 0 2 76 and 2 56 respectively Blood cholesterol was 446 and 480 mgm per 100 c c Albuminuria was somewhat less after 1 week in the hospital and after discharge decreased further and then disappeared

On admission to Harvard University in Sept 1933 there was no edema and the urine had specific gravity 1 0 0 no albumin no cells had no casts His blood pressure was 110/70 In June 1934 the findings were the same

Dec 17 1934 he was admitted to the Stillman Infirmary because of malaise and anorexia which developed without any prior infection or infectious disease Again there was edema and much albumin in the urine occasional red cell white cell and casts with specific gravity 1 014 to 1 028 Total protein was 4 5 gm with albumin 2 and globulin 2 5 Cholesterol was 580 mgm per 100 c c of blood

Jan 1935 readmitted to Stillman Infirmary with mild impetigo Edema previously present disappeared as impetigo cleared Urine continued to show much albumin but on March 3 1935 this was much less

From May 9 to Sept 11 1935 six urine examinations showed specific gravity 1 020–1 028 no albumin no casts no red and no white cells Non protein nitrogen was 26–31 mgm per 100 c c of blood Plasma protein was 5 4 gm with albumin 3 3 and globulin 2 1 and 5 7 gm with albumin 4 0 and globulin 1 7 Blood cholesterol was 114–178 mgm per 100 c.c Blood pressure was 98/60 and 110/70

Feb 10 1936 following a cold and sore throat urine with specific gravity of 1 025 showed a slight amount of albumin and 2–3 red and white cells per high power field

Feb 12 1936 to Sept 9 1936 seven urine examinations showed specific gravity 1 024–1 030 no albumin no cells no casts Blood showed non protein nitrogen 30 mgm plasma protein 6 82 gm cholesterol 145–187 mgm hemoglobin 90 per cent Blood pressure was 100–110/60

May 19 1937 urine showed slight postural albuminuria no cells no casts Blood showed non protein nitrogen 31–37 mgm plasma protein 6 07–7 27 gm cholesterol 173–230 mgm

June 10 1937 to July 22 1938 ten urine examinations showed no albumin with negative tests for postural albuminuria In April 1938 for 4 days there was streptococcic sore throat and in July 1938 acute suppurative appendicitis with appendectomy, neither caused albuminuria except a slight amount day after operation

July 26 1938 to April 1943 eleven urine examinations showed specific gravity 1 018 to 1 030 no albumin with negative tests for postural albuminuria no cell, no casts

March 1 1945 to Aug 2 1946 — In Army service, Mch 1–2 boil on wrist given 150 000 units penicillin with prompt relief Mch 23 1945 edema of face and eye lid and generalized anasarca Mch 23 1945 to Aug 2 1945 five urine examinations showed specific gravity 1 023–1 028 very large amount of albumin but no cells, no casts Blood plasma protein was 5 04 gm and blood cholesterol 588 mgm Blood pressure 1 0/80 Army discharge diagnosis nephritis chronic

Jan 30 and 31 1946 seven urine examinations showed no albumin by clinical tests including negative tests for postural albuminuria no cells no casts Chemical quantitation of albumin in these specimens showed 3–7 mgm which is normal At this time blood non protein nitrogen was 23 mgm blood plasma protein 8 4 gm with albumin 5 2 and globulin 3 2 blood cholesterol 356 mgm Blood pressure was 110/70 and general physical examination was negative except for dry scaling lesion on wrists Patient feels and seems well

Summary of Case XI — A boy of 17 in 1933 without any evident etiological factor had Bright s disease of the edematous type (nephrotic syndrome) In 1934–35 there was a recurrence In 1945 there was a second recurrence In between these attacks edema disappeared urine became normal and plasma protein and cholesterol levels returned to normal or were only moderately abnormal Even in the acute phases red blood cells appeared in the urine only in very small number and that in the 2nd and 3rd attacks The same was true of white cells and casts Never was there any hypertension or nitrogen retention In each attack blood plasma protein decreased with globulin increased in ratio to albumin blood cholesterol increased The third attack followed a boil, but patient has had other infections including streptococcic sore throat and appendicitis without return of edema and albuminuria The interval and present normality of urine is a striking feature Most careful recent studies show a normal physical examination normal urine and normal renal function 13 years after beginning of first attack There is some factor giving this patient an unusual predisposition to attacks of Bright s disease of the edematous or nephrotic type Are the kidneys now normal? Careful study shows no abnormality in their function The author believes that the glomeruli now no longer are structurally entirely normal although seemingly completely normal in function in his opinion recurrence is probable with eventual progression into some form of chronic Bright s disease Whether this is a correct assumption or not subsequent developments will tell, if the patient remains alive and can be followed by periodic examinations

Case XII — A woman of 50 Med No 7773 was in the hospital eight times as follows December 29 1917 to February 15 1918 March 26 1918 to September 28 1918 November 14 to 27 1918 April 9 to 10 May 8 to 29 and August 25 to 31 1918 April 10 to 22 1922 October 3 to October 9 1932 and November 6 to November 20 1936 when she died As a child she had had mild whooping cough measles and mumps and grippe 21 years ago otherwise she had been healthy always

History — About two years ago (1915) her feet began to swell slightly in the evening This would always disappear by the next morning She also began to have nocturia about one time each night The swelling of the feet became gradually worse up to May 1917 and the swelling did not go down over night They became so large that she could not get her shoes on She would have to sit with her feet on a chair all day long to keep them from swelling and paining About 4 months ago the swelling became much worse her abdomen began to swell slightly and 10 weeks ago the swelling became so bad that she had to go to bed She has remained in bed ever since About 6 days ago she felt somewhat nauseated and noticed that her urine was becoming scant so that she has not passed over a pint and a half of urine a day for the last six days At no time has she had any blurring of vision or headaches and she never noticed blood in her urine She has not had nausea and vomiting except as mentioned She comes in for relief of the swelling

Physical examination showed puffiness of lower eyelids and whole face legs and trunk up to mid thorax were very edematous the abdomen was distended with fluid and gas Heart and blood vessels were normal Blood pressure was 140 mm Hg systolic and 110 diastolic Her urine (see Table IX) had a specific gravity of 1 030 a large amount of albumin a few to numberous hyaline and granular casts a few red blood cells very slight amount of chloride and a phthalein excretion of 45 per cent in two hours

During the periods of hospital observations down to August 1919 edema and ascites have always been present varying in degree from time to time Abdominal fluid frequently has required mechanical removal The remarkable thing has been the relatively little variation in her condition between December 29 1917 and March 30 1920 with on the whole improvement in the average condition as time has gone on so that on March 30 1920 although still showing edema there was no demonstrable ascites and renal function was unchanged Up to then eye grounds had not shown edema hemorrhage or exudate Repeated blood pressure observations had shown variations in pressure but no hypertension There had been no anemia at times with slight infections there had been moderate leucocytosis The urine and renal function (see Table IX) had remained remarkably constant with a tendency for albumin to decrease in amount Phthalein excretion had remained fairly good and fluctuated little blood urea nitrogen had been normal except when protein intake was large and then increased only moderately

In May 1910 she had an attack of lobar pneumonia without any exacerbation of her Bright s disease For 7 months following discharge from the hospital on August 31 1919 she was up and about daily feeling extraordinarily well and her edema lessened Then she caught cold and following this became weak and drowsy with urinous breath. The drowsiness lasted 8 days and she had frequent twitchings of *arms and legs and*

TABLL IX

URINL LXAMINATIONS AND TESTS OF RENAL LUNCTION CASE XII

Date	24 Hr 1 ml	Sp Gr	Alb	Casts Hy	Casts Gran	Casts Cell	A B C	H B C	Ph	B U N	Bl Cl	Wt
1917				*			**	*				
Dec 30	425	1 030	++					++				62 0
Dec 31	1 025								53ʻ o	11 9	4 98	63 0
1918												
Jan 1	900	1 011	+++	+	+		+	+				63 0
Jan 7	825	1 022	++	+++	+++			++				60 2
Jan 11	,00	1 017	++	++	++			++		10 8	5 03	60 2
Jan 13	1 125	1 012	+++					+				60 2
Jan 14	1 300								45ʻ o			60 0
Jan 16	725	1 010	++						14ʻ c	6 6	5 28	59 0
Jan 17	1 275	1 013	++									59 0
Jan 18	1 375	1 014	++		+			++				59 0
Jan 21	1 129	1 013	++	+	+			+				57 8
Jan 22												57 2
Jan 23									48 c	4 9	4 84	57 0
Jan 24		1 010	++	++	+			++				56 8
Jan 27		1 022	++	+				++				56 6
Feb 10		1 013	++	+				++				54 2
Mar 26	180	1 030	++		+			++++++	37ʻ o	12 7		60 4
Mar 28		1 015	+	+++			+	++++++				59 4
Mar 29	625											58 4
Mar 30									28 o			
Apr 1		1 028	++	+	+			++++				59 4
Apr 3			++	++	+		+			9 8	5 03	58 8
Apr 4	350	1 025	++					+++++				59 0
Apr 8	340	1 017	++	+++			+	+				58 6
Apr 11	344											58 5
Apr 12	700	1 022	++	++	++		+++	++	56 o	7 3	5 11	58 5
Apr 15	572	1 019	++	+	+		+	++				59 2
Apr 18	440	1 017	++	+	+			+++	43ʻ o	8 6	5 36	59 6
Apr 22	318	1 023	++	++	++++			+++				60 0
Apr 24	318	1 021	++	++	+		+	+++	(30 c c) 11	8 5	5 55	60 0

TABLE IX (Cont)

URINE EXAMINATIONS AND TESTS OF RENAL FUNCTION CASE XII

Date	24 Hr Amt	Sp Gr	Alb	Casts			R B C	W B C	Ph	B U N	Bl Cl	Wt
				Hy	Gran	Cell						
1918							•					
Apr 29	348	1 024	++	++	+			++	(50 c c) 45%	8 5	5 00	61 1
May 6	293	1 022	+++	++	+		+++	++				61 2
May 8	398								42%	8 7 Asc Fl	Plasma Cl	
										8 6	6 06	61 1
May 29	358								34%	8 0	5 33	59 4
May 30	448	1 019	++	+++++		+		+++				60 0
June 14	380	1 029	++	+++	+++			+++				61 0
June 18									54%	0 0	5 80	60 8
Jun 20		1 019	+++	+++		+	+	++++				61 6
June 26	495								45%	9 2	5 36	55 4
June 27	480	1 025	+++	++	+			+++				55 0
July 29	469	1 021	+++	+++	+		+	+++				
July 30	276								(35 c c) 36%	Plasma U N	Plasma Cl	
Aug 7	600									20 0	6 31	
Aug 8	803	1 018	+++	+	+			+++	36%	20 7	5 43	
Aug 28												56 0
Aug 30	441	1 022	+++	++	+			++	34%	17 7	5 01	62 8
Sept 15	68	1 015	++	+	+++		+	+++				57 8
Sept 16												51 6
										12 5		51 8
Nov 17	240	1 022	+++	+	+		+++	+++				59 0
Nov 21	398	1 018	+++	++				++	40%	22 0	5 13	53 0

TABLE IX (Cont)

URINE EXAMINATIONS AND TESTS OF RENAL FUNCTION CASE XII

Date	24 Hr Amt	Sp Gr	Hb	Casts Hy	Casts Gran	Casts Cell	R B C	W B C	I h	B I N	Bl Cl	Wt
1919					*	*						
Apr 10	342	1 027	+++	++	+			++++				53 4
Apr 11	395								35 cc	27 0	4 63	
Apr 17		1 019	++	+			+	++	40 cc	15 0	4 88	
										A cit	Ascit	
										ic fl	ic fl	
										16 0	6 03	
May 9	400								40 cc	11 0	4 84	68 0
May 11	705	1 019	++	+++				++				
Aug 25		1 020	+	++			++	++				51 4
Aug 28	1 125								10 cc	13 0		50 4
1920												
Mar 30	1 500	1 016	++++	++				++	24 cc	17 0		
Apr 23	S S	1 018	+++						24 cc	17 0	5 54	
May 21	S S	1 018	+++	+++			+	+++				
Aug 11	S S	1 014	++									
Nov 24	?	1 016	+++	+				+++++	? 20 cc	18 0	5 63	
1920												
Dec 17	1 000+	1 008	+++	+				+++				
1921												
Aug 24	3 pts	1 020	+++	++			+	+++++	35 cc	19 0	5 45	
1922												
Jan 17	750	1 022	+++	+				+++				
Mar 31	S S	1 018	++				+	++++				
Apr 3	2 000	1 008	++					+++				
Apr 8	S S	1 009	++					++++				
Apr 10									30 cc	15 0		
June 14	?	1 014	++	+				++				
July 12												58 0

TABLE IX (Cont)

URINE EXAMINATIONS AND TESTS OF RENAL FUNCTION CASE XII

Date	24 Hr Amt	Sp Gr	Alb	Casts			R B C	W B C	Ph	B U N	Bl Cl	Wt
				Hy	Gran	Cell						
1923												
May 23	1 000+	1 017	++	+++				++				58 6
May 31	1 000	1 025	++	+			+	++	25 %	11 0	4 95	
June 16	S S	1 023	+++	+++				+				
Dec 12	1 125	1 020	++					+++	34	11 0	4 93	58 0
Dec 14									53 %			
1924												
Mar 26	1 000	1 020	++	+			+	+				60 0
Apr 7		1 023	+				+	+	30 %			
June 25										17 0	5 2	
1932												
Oct 3									65%			
1935		1 018	+						40 %	20 0		
1936												
May									s p t	30 0		
Oct									0	34 0		
Nov 6	700	1 016	+++						0	40 0	5 60	
Nov 8	475	1 012	++++						0	53 0		49 8
Nov 17									0	80 0		

Sp Gr = Specific gravity Alb = Albumin Hy = Hyaline Gran = Granular Cell = Cellular R B C = Red blood cells W B C = White blood cell Ph = Phenolsulphonephthalein excretion in two hours B U N = Blood urea nitrogen in milligrams per 100 c c of blood Bl Cl = Blood chloride in grams per liter of blood Wt = Weight in kilos

+ = Very slight trace of albumin
++ = Slight trace of albumin
+++ = Much albumin
++++ = Very much albumin

** = Rare
++ = Numerous
+++ = Many
++++ = Very many
+++++ = Very very many

occasional headaches Her blood pressure which usually had been normal rose to 196 mm Hg systolic and 118 mm diastolic She soon recovered from this attack, and shortly afterwards her phthalein was 24 per cent and blood urea nitrogen 17 mgm per 100 c c of blood During the following 2 years her activities increased Casts decreased and finally disappeared from her urine, albumin and white cells persisted Blood urea nitrogen returned to normal and phthalein ranged about 30 to 35 per cent The blood pressure was often above normal Arteriosclerosis was demonstrable in retinal vessels Edema although less than formerly, usually was found to be present

On April 10, 1922 the patient was admitted to the hospital for the seventh time in 5 years This time she entered because of frequent and painful urination associated with an acute pyelitis Physical examination aside from pallor and slight pitting edema of the shins was negative Blood pressure was 155 systolic mm Hg and 80 mm diastolic Urine (Table IX) showed a trace of albumin very numerous white cells many fine and coarse brown granular casts and an occasional red cell Phthalein was 30 per cent, and the blood urea nitrogen was 15 mgm per 100 c c of blood She stayed in the hospital 12 days She received bladder irrigations and installations of argyrol which caused considerable improvement During her stay in the hospital she developed an absolutely irregular heart action and extensive edema of the back, legs and abdomen This irregularity disappeared and the patient was discharged improved although the urine still contained a trace of albumin numerous white cells and a rare hyaline and granular cast

One year later 1923 the patient came to the Outdoor Department complaining of much pain in the left flank She had dyspnea upon exertion and slight edema of the shins after being on her feet Urine output was about one quart in 24 hours phthalein excretion 25 per cent and blood urea nitrogen 11 mgm per 100 c c of blood (Table IX) The blood pressure was 161 mm Hg systolic and 98 mm diastolic The urine showed a trace of albumin rare to numerous hyaline casts and many round cells and white blood cells and a rare red blood cell Since these observations were made the patient was seen at irregular intervals in 1924 Her worst trouble now was cystitis Edema was still present phthalein had risen to 53 per cent Blood pressure had returned to normal and although cystitis caused her considerable trouble in the way of discomfort her kidney condition was remarkably better

She was seen in the Outdoor Department several times during the last 3 years and symptoms changed but slightly there had been no ascites very occasional nosebleeds She had begun to complain of blurring of vision by 1926 By April 1928 her blood pressure had risen to 156 mm Hg systolic 100 disatolic she looked anemic had no strength and complained of bleeding from vagina and rectum but had no actual anemia During this period she developed a gradually increasing scoliosis By the last of 1929 she had an increasing nocturia her heart showed left ventricular preponderance with premature beats in the electrocardiogram and by x ray seemed a little larger In October 1932 she fractured her left humerus came to the hospital and got a good result

In January 1935 phthalein dropped to 40 per cent blood urea nitrogen was [illegible] mgm per 100 c c, her total protein was 5 5 grams per liter Her liver became palpable By May 1936 her phthalein had dropped to the slightest possible trace blood urea ni

trogen was 30 mgm per 100 c c her hemoglobin was 58 c red cell count 3 000 000 Edema did appear in her legs and then disappeared On October 8 1936 her phthalein was 0 her blood urea nitrogen 34 mgm per 100 c c her hemoglobin 55% red cell count 2 740 000

She was admitted to the hospital the last time on November 6 1936 She was now a small poorly developed old lady in no obvious distress but extremely irritable mentally with a dry pale skin coated tongue uriniferous breath Ophthalmoscopic examination showed moderate arteriolar sclerosis with no hemorrhages no papillary edema She now had a marked scoliosis Her blood urea nitrogen ranged between 18 and 40 mgm per 100 c c phthalein continued at 0 she showed evidences of acidosis and remained in an unconscious or a semi stuporous state On November 17th her urea nitrogen had risen to 80 mgm per 100 c c her Co_2 had dropped to 27 per cent total protein was 5 1 with 2 5 albumin and 2 6 globulin Her hemoglobin dropped to 45 per cent the red cell count to 2 390 000 and he developed leucocytosis from 15 000 to 21 000 She died on November oth 1936

Autopsy diagnoses were glomerulonephritis chronic bronchopneumonia right cystitis acute kyphosis marked The heart weighed 300 gram and seemed normal Coronary arteries showed only a little yellowish atheromatous change Kidneys weighed 60 grams each with apparently dilated pelves and a finely granular surface with adherent capsules that did not appear abnormal On cross section the cortex was reduced to 3 mm pyramids were darker than the cortex and the superior pole of the left kidney showed numerous cysts from ½ to 1½ cm in diameter

On microscopic section there was no leucocytic infiltration glomeruli and tubules were markedly changed a normal appearing glomerulus was very exceptional many of them were reduced to masses of hyaline connective tissue in others the capillary loop were partly preserved but the sub-capsular space was obliterated In the best preserved ones the capillary loops contained moderate amounts of blood but the basal membrane usually was thickened and the sub-scapular spaces patent containing small amounts of albuminous material The tubules showed varying degrees of change some were large dilated with atrophic epithelium others were atrophic Interstitial connective tissue was increased diffusely The arteries presented considerable thickening of their walls the larger vessel showed considerable intimal proliferation often with extensive splitting and reduplication of the internal elastic lamina Their media however was well preserved

Summary of Case VII — A woman of 50 years in 1915 developed edema of her feet which gradually increased in amount at first it disappeared over night later it was constant The urine decreased in amount with much albumin hyaline and rarely granular casts leucocytes and occasionally rare red blood cells No infectious disease or infection had occurred as a possible etiological factor After about o months the abdomen became swollen Edema and ascites long persisted as the prominent feature of the case but gradually the ascites disappeared and the edema although persisting decreased and after 13 years finally disappeared Latterly on occasions granular casts have been found in the urine There never

occasional headaches Her blood pressure which usually had been normal rose to 196 mm Hg systolic and 118 mm diastolic She soon recovered from this attack and shortly afterwards her 'phthalein was 24 per cent and blood urea nitrogen 17 mgm per 100 c c of blood During the following 2 years her activities increased Casts decreased and finally disappeared from her urine albumin and white cells persisted Blood urea nitrogen returned to normal and phthalein ranged about 30 to 35 per cent. The blood pressure was often above normal Arteriosclerosis was demonstrable in retinal vessels Edema although less than formerly usually was found to be present.

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In January 1935 phthalein dropped to 40 per cent blood urea nitrogen was 0 mgm per 100 c c her total protein was 5 5 grams per liter Her liver became palpable By May 1936 her phthalein had dropped to the slightest possible trace blood urea ni

Edema

The dominant feature in these patients is edema, generalized and extensive of the subcutaneous tissue With this often goes an accumulation of fluid in the serous cavities ascites frequently is marked and causes abdominal discomfort and respiratory disability the latter often accentuated by bilateral hydrothorax These fluid accumulations frequently have an opalescent chyliform appearance Edema fluid has a very low content in protein[31] but usually there is an increased amount of sodium chloride in it The patient looks pale with puffy face swollen extremities and distended abdomen Although pale in appearance there is no actual anemia and often even after the disease has persisted for a long time hemoglobin and red blood cell count remain almost normal Moderate dyspnea is seen often due partly to the distended abdomen partly to pleural fluid partly to pericardial fluid and partly to pulmonary edema rarely the pulmonary edema is very marked

Interestingly except for some effect from edema of the lungs edema in other viscera very often is productive of few symptoms An exception is the occasional patient in which edema in certain locations is productive of particular annoyance or even serious symptoms Edema of the penis may be so extensive as to interfere with urination Edema in dependent parts may cause much discomfort from tension or even lead to rupture of the skin with the incident danger of infection Long continued edema in these regions often causes a chronic eczema of the skin Edema about the eyes may prevent opening the eyes Edema of the conjunctiva causes a disagreeable lachrymation or the swollen conjunctiva may even prevent complete closure of the eyes Edema of the eyes may cause indirectly an annoying low grade conjunctivitis Edema of the retina or of the optic nerve may decrease vision Edema of the larynx may interfere with respiration Edema of the uvula is often annoying the elongated uvula causing tickling in the throat Edema of the tongue and mucous membranes of the mouth may hinder deglutition and in decreasing taste sensation render the food unappetizing Edema of the tissues of the neck may become great enough to cause dyspnea Edema of the brain may lead to the symptoms attributable to increased intracranial pressure and even lead to the erroneous diagnosis of cerebral tumor At other times cerebral edema seems responsible for the stupor and coma interpreted as the result of uremia Edema of the lungs may cause a profuse watery sputum with dyspnea and very occasionally literally drown the patient Edema of the gastrointestinal tract causes digestive disturbances hinders peristalsis or causes diarrhea and sometimes causes symptoms suggestive of an abdominal lesion seemingly suitable for surgical treatment by operation Fluid in the pleura pericardium or abdomen causes the same train of symptoms due to fluid in these places of other origin

was gross hematuria Renal function as measured by 'phthalein and blood urea nitrogen varied but little from normal during seventeen years of observation (1917 to 1934) In 1935 20 years after onset of edema and 13 years after edema had disappeared, 'phthalein excretion began to fall and in 1936 reached zero while blood urea nitrogen rose to 20, 34, 40 and 80 mgm per 100 c c In 1919 her blood pressure following an attack of pneumonia rose to 196/118, then fell much but never again was normal In 1922 it was 155/80, in 1923 161/98 in 1928 155/100 In 1919 she had pneumonia in 1922 pyelitis and cystitis, which subsided but never disappeared but from time to time exacerbated In her later years she had circulatory insufficiency, at times congestive failure In her later years she developed an increasing scoliosis She died Nov 20 1936 21 years after her Bright s disease began she had small kidneys showing chronic progressive glomerular lesions as primarily the pathological process with which, however, vascular lesions were associated, the latter in part in compensation for kidney atrophy This is an example of chronic edematous Bright s disease commencing insidiously with edema and albuminuria long (13 years) continuing as an edematous type of chronic Bright s disease and then shifting to a non edematous type with a total duration of 21 years

Onset

Onset usually is insidious in the sense that without antecedent symptoms or with only slight malaise edema appears and gradually or rapidly increases In numerous patients there has been no definite antecedent infection or infectious disease so far as the patient knows in some as is the case with the hemorrhagic type of acute Bright's disease there has been a previous infection or infectious disease, usually mild Careful histories do often show that there was an infectious process a considerable time before the appearance of the edema and that in the interval between the infectious process and the appearance of the edema the patient has felt below par This form of observation suggests that numerous patients do begin their Bright s disease of this type with an infectious process as the etiological factor

An occasional patient begins like the hemorrhagic type of acute Bright s disease with blood in the urine but differs from this condition in showing a rapidly increasing edema and a decrease in blood in the urine with persistence often in increasing amount of albumin in the urine In the majority of the patients edema is noted first in face or legs or both In a few patients swelling of the abdomen is noted before edema appears in subcutaneous tissues In very many of the patients moderate malaise is the sole symptom In a few nausea may occur early Fever is exceptional throughout the course of the disease except in the crises ' to be described later

blood cells may be absent often they are present in small numbers sometimes in considerable numbers but enough to cause gross hematuria is a very rare finding Leucocytes are fairly numerous Casts are abundant granular for the most part but rarely they are absent In an alkaline urine casts may have disappeared Lipoid droplets often doubly refractile may be frequent few or absent as a rule some are seen Sodium chloride is decreased in amount often so much as to give no cloud from added nitrate of silver Calcium is almost absent from the urine also Phenolsulfonephthalein excretion continues normal or only moderately decreased even in the presence of marked oliguria sometimes it is actually increased beyond the average normal When it is more than slightly decreased progression into the non-edematous form of chronic Bright s disease is very probable Slight glycosuria is not very infrequent

The blood as already described in Part I shows *a considerable decrease in* plasma protein with the fall taking place in the albumins thus causing a shift downward in the normal albumin globulin ratio Electrophoresis technic applied in these patients shows the distribution of the albumins and the globulins in the blood plasma and urine of these patients (see Figs 5 6 7 38 and 39) Sometimes the plasma protein is not decreased in amount because of an increase in the globulin rarely this change may be sufficient to cause a plasma protein above average normal level Plasma chloride usually is increased but not always even when urine chloride is much reduced Plasma calcium often is reduced Blood lipoids chiefly cholesterol tend to increase Lipemia is frequent the serum may be milky Non protein constituents of the blood remain within normal levels in most patients except in crises in which a decrease of amino acids is found [345] Cell constituents of the blood usually are normal moderate decrease in red blood cells and hemoglobin may occur In acute cases there may be moderate leucocytosis

Crises

During the course of disease in patients of this group a very interesting phenomenon appears with considerable frequency Abruptly fever develops A large patch of reddening of the skin may appear particularly often over the upper inner surface of the thigh this strikingly resembles erysipelas on an already edematous skin There may be reddish streaks from it towards the groin and lymph nodes in the groin region become slightly swollen and slightly tender In other patients abdominal tenderness pain and muscle spasm may develop indicative of peritonitis often this actually is present and there has appeared a fibrinous exudate with leucocytes in the already existent abdominal fluid In this fluid no organism may be found or there may be bacteria most often pneumococci Sometimes following the erysipeloid type of skin inflammation positive blood

Edema gives to the patient a very characteristic appearance He is pale and pasty skin folds that give facial expression are lacking, his eyes water, he is, truly, a sad picture His skin is tense, often shiny in appearance where most swollen, in places it may be in folds Sometimes the skin bursts and exudes a thin serous fluid In the very loose areolar tissues such as those beneath the eyes and about the penis and vulva there may be a curious, gelatinous, semi translucent appearance In the most swollen parts there is no evidence of vascularity of the skin, and even on incision there is almost no bleeding

Other Clinical Features

Blood pressure rarely is elevated above normal until a progression into chronic Bright s disease without edema is under way as described later under the heading "Course of Disease" The *heart* remains normal to physical examination except in the unusual patient with sufficient hydropericardium to cause the usual symptoms and physical signs of pericardial effusion This absence of cardiovascular signs and symptoms in the presence of marked edema is a very striking feature

Toxic symptoms are strikingly absent except in the *crises* to be described later on in this section *Basal metabolism* with few exceptions is lowered, often as low as minus 35 to 50 per cent as in true and marked myxedema Besides edema already mentioned, *ophthalmoscopic examination* as a rule, shows no changes until progression into chronic Bright's disease without edema is well under way, a sequence taking place in numerous patients

By x ray bones in these patients show decalcification as already described in Part I In growing children with this form of Bright s disease growth is not disturbed Calcium deposition is defective in the shaft of the bones but is not defective in the epiphyses where growth of bone takes place Except for rarefaction these bones show no other lesions Rarely a spontaneous fracture has occurred in the calcium defective bones of these patients If these patients have a remission with disappearance of edema redeposition of calcium in the bones takes place[27], and they return to their normal x ray appearance

Urine and Blood

Urine is decreased in amount sometimes markedly, at times to anuria Specific gravity runs from 1 017 to 1 030, increasing as the amount of urine decreases and influenced by the amount of albumin Albuminuria is marked, sometimes enough with the heat acetic acid test for the urine to boil solidly and then the precipitate settles out as coarse white or grayish white coagula Globulin as described in Part I, is present in the urine as a rule in only small amount fibrin is more abundant while albumin is the chief constituent of the proteinuria Red

blood cells may be absent often they are present in small numbers sometimes in considerable numbers but enough to cause gross hematuria is a very rare finding Leucocytes are fairly numerous Casts are abundant granular for the most part but rarely they are absent In an alkaline urine casts may have disappeared Lipoid droplets often doubly refractile may be frequent few or absent as a rule some are seen Sodium chloride is decreased in amount often so much as to give no cloud from added nitrate of silver Calcium is almost absent from the urine also Phenolsulfonephthalein excretion continues normal or only moderately decreased even in the presence of marked oliguria sometimes it is actually increased beyond the average normal When it is more than slightly decreased progression into the non-edematous form of chronic Bright s disease is very probable Slight glycosuria is not very infrequent

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cultures are obtained More often this happens when peritonitis develops The pneumococcus is the organism found most often in blood cultures, but the streptococcus occurs, and infrequently other bacteria are found Moderate to considerable leucocytosis is usual during such crises

The phenomenon just described frequently is called a crisis or nephrotic crisis Study of the blood of these patients indicates that such crises are preceded by a fall in the amino acid nitrogen level of the blood plasma[315] If this fall in amino acids is prevented by the parenteral use of material rich in amino acids it is claimed that such crises can be prevented, or if they have occurred, such treat ment will shorten them decrease their severity and greatly minimize their other wise poor prognosis[345] The critical level of blood amino acid nitrogen appears to be about 2 5 mgm per 100 c c It is below this level that the crisis occurs Of course if there is evidence of the presence of the bacteria mentioned in the preceding paragraph then an appropriate sulfonamide or penicillin should be given As the kidney already is damaged, a sulfonamide should be given with great caution For this reason penicillin would seem to be preferable

Clinical Course

There is much variation in what happens to patients whose Bright's disease is dominated by heavy albuminuria and extensive edema lasting more than a few days Some recover completely among adults these are very few in number, among children a considerable number appear to recover as shown in statistics cited in the section on Prognosis which follows If recovery does not occur, the clinical picture may continue with very little change, this is infrequent especially in adults In some not many periodic decrease or even disappearance of edema may be seen with return at varying lengths of time to the situation in which edema dominates the clinical picture

The more usual sequence is for the edema to recede gradually and then dis appear While this is happening albumin decreases in the urine blood pressure gradually rises phenolsulfonephthalein slowly decreases anemia begins to appear and advances slowly and finally non nitrogenous proteins increases in the blood plasma For quite a long time such a patient would be classified as a case of chronic Bright s disease without edema indistinguishable on clinical examination from other patients in whom the process has developed from other beginnings as is discussed in a later section describing chronic non edematous Bright's disease Often in these patients heart hypertrophy develops with subsequent congestive failure and peripheral edema Thus edema of another sort cardiac edema, has appeared in a patient in whom there was present an earlier edema, a renal edema In many of these patients eventually appears the phenomena of uremia

In the edematous stage these patients are vulnerable to infections and die

from them Some of these infections are part of the so called crises described already under that heading others probably are not associated with a decrease in plasma amino acids

Prognosis

In this type of Bright s disease i e in the presence of extensive edema and marked albuminuria unless in a few weeks the edema clears up the albuminuria greatly lessens and the blood pressure does not rise prognosis is poor It is in children that recovery occurs most frequently in them recovery is fairly common In adults complete recovery is infrequent although there may be a long period of comparatively good health before the advent of a steadily progressing chronic Bright s disease Some patients die within a few weeks Others develop a fatal crisis during the course of an otherwise unchanging disease Some progress steadily into chronic Bright s disease resulting fatally in one to several years In some of the recovered cases recovery is deceptive for the disease has become latent and after months have passed evidence of chronic Bright s disease will appear

Statistics of prognosis are not satisfactory In children Davison and Salinger report a mortality of 32 per cent Clausen 43 per cent Blackfan and McKhann 38 per cent Davison and Salinger state their complete recoveries as 20 per cent Schwarz and Kohn as 25 per cent in chronic nephrosis in children In adults prognosis is far less good Fishberg stating that in adults with chronic nephrosis (in his classification he has neither acute or subacute nephrosis only chronic nephrosis) he has had no complete recoveries In contrast to this is the statement of Atchley[116] that the prognosis of true nephrosis is relatively good defining it as a chronic disease of variable duration in which the nephrotic syndrome exists without evidence of glomerulonephritis or amyloid disease According to Atchley this is a rare disease in adults with this I agree so rare that I never have seen but one adult patient with the criteria during life justifying the term true nephrosis and this patient at autopsy had much to my surprise idiopathic amyloidosis of kidneys liver and spleen

From the preceding it would seem that with the nephrotic syndrome prognosis is poor, unless the urine contains no or very few red blood cells and the blood pressure remains normal or only slightly elevated and that in adults very few patients with the nephrotic type of Bright s disease show these findings thus leaving a poor prognosis for all the others and these are the many among the adults while in children a considerable number do have these findings and so this type of Bright s disease in children has a relatively good prognosis which probably will be much better when crises are treated as indicated on a previous page under the heading Crises

Diagnosis

Diagnosis of the edematous types of Bright's disease, i e, of patients showing the nephrotic syndrome, with rare exceptions presents no difficulty The extensive edema the rich albuminuria and cylindruria, the paucity of red blood cells in the urine the absence of heart hypertrophy, the insidious onset and the disproportionate slight symptoms make a characteristic clinical picture which in itself is diagnostic Amyloidosis in some patients will present the identical clinical picture Amyloidosis should be suspected in the presence of chronic inflammation especially of lungs pleura and bones, of syphilis and of extensive neoplasm Amyloidosis occurs also in the absence of any of these conditions so-called idiopathic amyloidosis If suspected, proof or disproof will be found in the congo red test which will be positive, i e a very large proportion of the congo red dye will leave the blood stream very rapidly, if amyloid deposit is extensive in the body It is to be remembered however, that the relatively large molecule of congo red can, and does pass through the glomerular membrane which in these patients is allowing the free passage of molecules of albumin So in these patients part of the congo red leaving the circulation may be going out through the kidney instead of being taken up by amyloid within the body, and this part found in the urine must be allowed for in interpreting the amount remaining in the circulation in varying periods following its intravenous injection The presence of an enlarged liver or spleen in itself in patients with this clinical appearance should suggest the presence of amyloidosis and cause the congo red test to be carried out

An unusual case of myxedema might be confused with this type of Bright's disease inasmuch as the myxedema in such a case might be so extensive as to suggest edema of renal origin In both conditions metabolic rate could be equally low and with the myxedema there might be a complicating renal disease to cause albuminuria or the albuminuria might arise from chronic passive congestion from a myxedema heart Actually I have seen such a patient come to the hospital with the diagnosis of ' nephrosis ' Giving proper amounts of thyroid gland substance promptly demonstrated that the condition was myxedema not Bright's disease It is very interesting that myxedema usually clears dramatically often with small amounts of thyroid 15 to 60 mgm (gr $\frac{1}{4}$ to 1) a day, while the low basal metabolism of this type of Bright s disease remains uninfluenced by large even huge doses of thyroid

There is a form of cardiac insufficiency with marked edema slow pulse rate regular rhythm and considerable albuminuria which not infrequently is mistaken for this form of Bright s disease the enlargement of the heart being overlooked Treatment with digitalis in these patients as a rule, causes marked diuresis and shows that cardiac, not renal insufficiency is the main cause of the extensive

edema Beriberi can produce the same clinical appearances the use of thiamin chloride in large doses will improve the condition in a way to indicate the correct diagnosis in these patients digitalis alone is apt to fail to bring a prompt diuresis

Hypoproteinemia of various causes including marked nutritional insufficiency will cause the same clinical appearances as found in this form of Bright s disease but without the characteristic albuminuria Anemia chronic infections hepatic insufficiency from various lesions of the liver chronic diarrhea prolonged vomiting are among recognized causes of hypoproteinemia In addition there is a rare case of hypoproteinemia in which no cause for it can be found With hypoproteinemia without renal lesion the mechanism of edema is essentially the same as in patients with the form of Bright s disease here under discussion These various forms of hypoproteinemia would not be accompanied by the marked albuminuria which goes with this form of Bright s disease

The proteinuria of multiple myeloma and sometimes of other bone neoplasms and rarely of leucemia might be mistaken for the albuminuria of Bright s disease If as infrequently occurs there is generalized edema either from associated anemia or from renal or cardiac disease the clinical picture of this form of Bright s disease may be practically duplicated The demonstration of Bence Jones protein or other abnormal protein in the urine which can be done by simple tests or better by electrophoretic analysis will make certain that the condition in a patient with x ray evidence of bone lesions or the blood of leucemia is not Bright s disease showing a nephrotic syndrome Confusion still might come in a very rare case since the presence of Bence Jones protein has been reported as a rare finding in the urine of patients with Bright s disease

Prophylaxis

What has been written for prophylaxis of the acute hemorrhagic type of Bright s disease applies to the type now under discussion except fewer patients recover completely

Treatment

The chief object of treatment of patients with the edematous type of Bright s disease is to reduce the edema while maintaining as good general nutrition as is possible and avoiding infections and other features likely to increase renal damage Bed rest is to be regarded as an advantageous general measure which also minimizes infections and other untoward features Edema reduction is sought directly by measures to remove excess fluid from the body and indirectly to influence it by measures to elevate the plasma albumin whose deficit is considered to be the

primal cause of edema Another important feature of treatment concerns the prevention and management of crises already discussed on a previous page

Bed Rest

Bed rest continued until edema abates markedly or until it seems evident that the condition is going to persist for a long time, is advised In the latter situation a time usually comes, when the patient s morale is decreasing, appetite is failing general condition of the patient is deteriorating, and the physician wonders whether periods out of bed with some physical activity may not better the situation or at least increase morale and make the patient happier Wisely observed trial of the effects of sitting up and moving about now are indicated Fortunately no immediate harm will come from such a trial Obviously, if this change of regime causes very great fatigue or discomfort from edema settling in dependent parts, it should be modified so as to reduce these features

What has been said already under treatment of the hemorrhagic type of acute Bright's disease as to an airy room, avoidance of drafts flannel garments etc is equally applicable in the management of the edematous type of Bright s disease

The amount and extent of the edema rather than the degree of albuminuria is the best index that we have of the patient's response to the rest regime and other therapeutic measures

Diet

For this type of Bright s disease diet should be generous and as complete in all factors as is possible, but salt restriction should be practiced Protein intake should be as high as the patient can take and digest appetite and the possibility of acquiring food aversions are considerations governing the actual, practical protein component of the diet, a goal of 100 gm of protein, largely meat protein, should be set more than 100 gm , however, is desirable Such diet is given in the hope that the patient's deficit in plasma albumin will be made up Unfortunately very often very slight sometimes no increase of plasma albumin results from such a diet High protein intake also is believed to lead to some diuresis by reason of the action of the increased urea that is formed Amino nitrogen compounds can be used orally or intravenously as a means to increase plasma protein level and to maintain nitrogen balance as indicated in the next paragraph

Amino acids can be used effectively in various conditions of malnutrition, including those of Bright's disease, as a source of plasma protein and to maintain nitrogen balance, as has been demonstrated both in animals and in man by Whipple and his associates[459] and by others Ten amino acids appear to be essential, these are threonine, valine leucine, isoleucine, lysine, tryptophane, phenyl

alanine methionine histidine and arginine These can be prepared in pure crystalline form and these and various impure commercial mixtures have been used At present the expense of the pure crystalline amino acids and the limited amounts of them available largely restrict their use to special studies Various commercial preparations containing amino acids usually made from hydrolysis of casein or soy bean are available however in form pure enough for parenteral usage and these have been utilized to maintain plasma protein and nitrogen balance in patients incapable of adequate nutrition by mouth For periods of as long as eight weeks parenteral nutrition mainly with amino acid preparations and glucose has sufficed for a patient[480]

From studies already published it seems evident that amino acids in pure or impure form are destined to have important clinical usage as additional nutriment by mouth or replacement nutriment subcutaneously or intravenously in patients who by reason of nausea and vomiting or from gastric or intestinal disease get insufficient food by mouth or who for one reason or another lose protein from the body or fail to metabolize it and in one or the other of these ways develop hypoproteinemia

Their parenteral use now is accompanied by infrequent and not serious reactions[481] Fever may follow but this happened only in 1 5 per cent of 550 infusions, fever was brief and not high Flushing of the face nausea and dizziness may occur especially with rapid injection These reactions are of the nature following other forms of intravenous injections A nitritoid reaction with sense of constriction in the chest pain in lumbar region headache and occasional nausea and vomiting may occur but only rarely In all only 22 reactions of any sort occurred in a series of 550 infusions of amino acid preparations and only rarely did they hinder the parenteral nutritional usage of amino acid preparations Such reactions which undoubtedly can be reduced in number by various precautions in their intravenous use are not frequent or severe enough to be any reason for not using them

Fluid Intake

As to fluid in the diet three views are held (1) the fluid intake should be restricted 1 000 to 1 200 c c each 24 hours (2) the fluid should be normal or moderately increased 1 500 to 2 500 c c each 24 hours (3) the fluid should be increased considerably beyond the usual normal intake averaging 4 000 c c or more each 24 hours

(1) Fluid intake according to the commonly accepted practice should be restricted to about 1 000 to 1 200 c c per day unless this leaves the patient uncomfortably thirsty If so fluid intake needs to be increased In hot weather 1 200 c c usually is insufficient but these patients sweat much less than normal

and so hot weather loss of fluid from the body is subnormal and calls for less fluid increment than would be expected When diarrhea or vomiting cause fluid loss, more fluid to balance this must be supplied, by mouth, if possible, if not, parenterally in the form of 5 to 10 per cent aqueous glucose solution, but not glucose in normal saline solution It must be kept in mind that even in the water logged patient dehydration may develop as shown by shriveled, dry red tongue, parched throat and pinched face, if it does develop more fluid to offset it must be given When marked diuresis happens, as sometimes it does more fluid needs to be given in proportion to that excreted by the kidney

(2) In contrast to the preceding view is the one that gives much more fluid, in amount 1 500 to 2 500 c c each 24 hours judging the amount very largely by the patient's feeling of thirst and the absence of increase in the edema as indicated by the patient's weight

(3) Another group believes that a considerably larger than average normal fluid intake should be advised, fluid intake of 4,000 c c or even much more, along with marked salt restriction

The author prefers to use the first plan in the beginning of treatment with full attention to the various conditions which have been cited calling for increase in the net fluid intake of 1 000 to 1,200 c c If this plan appears to produce little decrease in the edema or is very irksome to the patient, then the author would shift to plan number 2

The kind of fluid given seems unimportant the patient can be allowed his preference as to water or various beverages including tea and coffee

Salt Intake

The view is held generally that for these patients with all diets and any fluid intake should go a restricted sodium chloride intake to the point of adding none in the preparation or serving of the food Some advise selecting the food so as to attain as low a salt intake as is possible Such diets to be reasonably palatable will contain about 2 gm of sodium chloride a day To many patients salt beyond this is craved and should be allowed when after trial the very low salt diet appears not to be influencing the edema There is a desirable psychological effect in allowing the patient to have a known limited amount of salt to shake on his food as his taste suggests Whatever degree of salt restriction is being carried out, a period trial of adding 5 gm of salt per day for several days is wise the author has observed that in some patients this has led to an increase in urine output Some of these patients have a urine almost devoid of chloride determined simply by adding to the urine a few drops of a solution of nitrate of silver, these patients are the ones most apt to do best on a very restricted salt intake but even this is not always the situation this is an additional reason for trial of varying degrees

of salt restriction rather than a theoretically fixed one in the management of this edematous type of Bright s disease Various substitutes for table salt sodium chloride have been tried but in general they have not proved satisfactory either to the physician or to the edematous patient and so they are not advised Potassium chloride has been used rather extensively in place of sodium chloride added to the food from a shaker A rare patient seems to like this practice and does well on it It may lead to an increased output of urine and o be useful There is a necessary caution to be applied in its use potassium chloride should not be given in this way to a patient with evidences of renal function poor beyond inefficiency in the excretion of water and sodium chloride because retained potassium is toxic and can be dangerous

Efforts to Increase Osmotic Pressure of the Circulating Blood

If the edema in these patients i due to decrease in plasma albumin as is generally conceded then edema will be controlled if the loss of albumin in the urine can be stopped or markedly decreased or if the deficient plasma albumin can be increased to a higher level or if some other material of similar molecular size can be added to and retained in the circulating blood to restore osmotic pressure to a level approximating that normal to the blood

We have no means of actually decreasing the albuminuria in these patients Occasionally it ceases as a result of a process of recovery More often it decreases with change in character of the glomerular lesion this happens as the process passes over into glomerulonephritis with the lesions of that pathological condition when the albuminuria becomes small in amount edema disappears unless during this process cardiac insufficiency has developed to cause edema of that origin To replace the albumin lost from the blood in patients with the edematous type of Bright s disease here under discussion in the usual case from 10 to even o gm of albumin must be added each 24 hours to offset that leaving the body through the kidney

It is to the end of increasing plasma albumin that the *high protein diet* already discussed is recommended Unfortunately it fails very often to do this and other measures are needed however to date none are very effective

Purified Human Albumin — It was believed by many that when albumin became available in pure form from human or other sources an albumin which would cause no untoward reaction after intravenous injection the problem of removing edema in these patients would have been solved Many of these probably failed to realize how much the daily albumin loss to the body was in these patients and hence how much purified human albumin would be needed to replace this loss to say nothing of what would be needed to lead to a steady rise in plasma protein level toward a normal figure The preparation from human

blood serum of pure albumin, which can be dissolved and injected intravenously in patients with hypoalbuminemia and edema, has been attained and its use has been tried in patients with the nephrotic type of Bright's disease[50, 351, 352], but so far therapeutic results have been disappointing with the amounts given, 25 to 50 gm daily Such albumin introduced intravenously in man disappears rapidly from the circulation and so has little prolonged influence in raising the osmotic pressure of the circulating blood and causing diuresis When with hypoproteinemia there is no or very slight albuminuria, the injected albumin passes quickly into the body tissues and is stored there When there is taking place a large loss of albumin into the urine as is usual in this form of Bright's disease, much of the injected albumin is excreted also in the urine Following injection of albumin there is a rise in plasma albumin soon after injection, an increase in osmotic pressure and an increase in plasma volume The rise in plasma albumin lasts only a few hours The increase in plasma volume renders dangerous the injection of large amounts of albumin, for fear of raising venous pressure and of causing serious pulmonary congestion So far the daily injection of 25 to 50 gms of albumin equivalent to 500 and 1 000 c c of blood plasma, into the circulation has been tried in a few patients with the edematous type of Bright s disease with negligible improvement except in small children, and even there the diuresis may have been coincidental

The relatively high sodium chloride content of the purified albumin used in the studies just discussed probably was an important factor in decreasing the diuresis obtained from its use For stability under field conditions, for which the concentrated normal human serum albumin was designed, a high salt sodium chloride concentration was adopted Believing this probably an adverse factor in ridding the body of edema fluid, a salt poor human albumin has been prepared, this has a sodium chloride content $\frac{1}{3}$ of that in this other form of purified human albumin which now may be called in contrast to this low salt form high salt human albumin Such salt poor human albumin has been used in a series of patients[3, 2] with better results so far as diuresis is concerned than that obtained from the high salt human albumin The salt poor human albumin was given in sterile dextrose solution so prepared as to contain 10 per cent albumin and 6 per cent dextrose In order to avoid any disturbance of the patient s circulatory mechanism, and this was accomplished, the albumin dextrose solution was given intravenously at a slow rate 100 c c per minute The daily dose contained 50 grams of albumin and 30 grams of dextrose in 500 c c of water this was given over a varying number of days during this study, 1 day and 3 10 22 and 30 successive days so that a given patient might receive 50 gm 150 gm, 500 gm 1100 gm and 1 500 gm of albumin in different sets of observations As is true in general of all diuretics the amount of diuresis was roughly in proportion to the amount of the edema Some observations indicated that albu

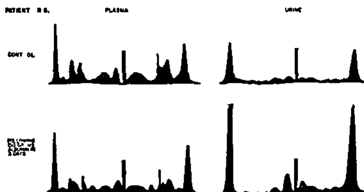


Fig 38 This shows the electrophoretic patterns of plasma and urine before and after intravenous injections of salt poor purified human albumin in a patient R S showing the nephrotic syndrome

min more than 50 gm a day was not proportionatel more effective as a diuretic agent and might be a strain on the circulation while 25 gm could not be depended upon to produce a satisfactory diuresis In a patient with massive edema a single day of receiving 50 gm of salt poor human albumin increased daily urine output from an average of 820 c c to 1630 c c and 2060 as highest and lowest When this treatment was repeated on successive days the daily diuresis was continued with a slight tendency to become a little less as the days went by and the patient s edema decreased in amount During the period of injection of the albumin solution urinary protein loss increased about one third but non protein nitrogen decreased and balance studies indicated a total gain in nitrogen varying in different patients and in relation to the total amount of albumin given the greatest retention of protein averaging 60 per cent of injected protein after 1 dose of 50 gm and 54 per cent after 3 doses of 50 gm Figures 38 and 39 show the changes caused in the electrophoretic patterns of two patients of this type Increase in protein excretion continued for several days following a period of albumin injection

The authors of this paper include the following statements The greatest use would appear to be in the extreme nephrotic stage In the edema free patient *tending toward a fixation of specific gravity nitrogen retention and hypertension* its value is less and occasionally its use may be contraindicated from the cardiovascular standpoint by reason of its ab lity to produce and maintain striking rises in blood volume

Indeed it is in extreme nephrosis, the edema of which is notoriously quite resistant to mercurial diuretics in which administration of amino acids has no constant effect and in which anorexia often prohibits oral urea in large doses that an agent, which will induce and maintain a diuresis may occasionally give dramatic symptomatic relief to a desperately sick patient

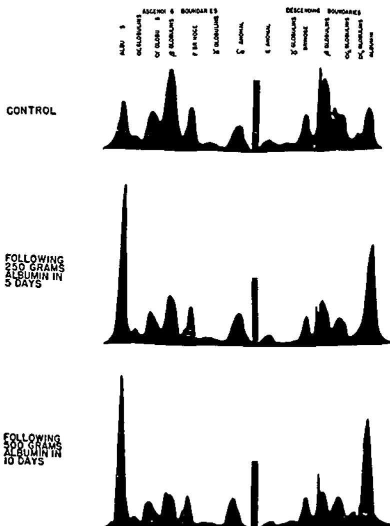


Fig 59 This shows the electrophoretic patterns of plasma before and after intravenous injections of salt poor purified human albumin in a patient W H showing the nephrotic syndrome

It is important to emphasize the basal dietary regimen of these patients in evaluating the ability of albumin to maintain diuresis and positive nitrogen balance Had not these patients been very close to positive nitrogen balance on the dietary intake alone larger quantities of albumin may well have been required to induce the significantly positive nitrogen balance attained and the feeling of well being that appeared to accompany that state Likewise, it is obvious that the rigid restriction of salt is important in the maintenance of diuresis with salt

poor albumin particularly in view of the possibility that salt poor albumin might have succeeded in the previously reported instances where high salt albumin has failed in attainment of diuresis

No evidence emerges from this study that the diuresis or positive nitrogen balance induced by salt poor albumin results in any change in the natural history of the disease process Clinical follow up studies have shown no deleterious changes in renal function ascribable to the relatively large doses of albumin '

It would seem that the necessarily limited supply of concentrated human albumin its great cost and the features just enumerated will prevent this form of treatment of edematous Bright s disease from being of great usefulness Its greatest value is its diuretic effect including a nutritive value of some importance It is to be emphasized again that it does not seem that salt poor human albumin more effective than the salt high preparation has shown any demon trated influence in changing the course of the disease process re ponsible for the clinical conditions encountered in Bright s disease with the nephrosis syndrome

Blood and Blood Plasma —Transfusions with these have been used the latter also in the form of redissolved dried plasma As already explained they have had results similar to those obtained from injections of albumin remembering that 500 c c of blood or plasma are equivalent to 25 gm of albumin in effect on plasma protein and on osmotic pressure Since patients with the edematous type of Bright s disease usually have only moderate anemia transfusion of whole blood has not the influence that it would have were there severe anemia Consequently in this form of Bright s disease there is to be expected little difference in effect between injections of whole blood and a solution of dried human blood plasma neither has proved to be of great help in the patients here under discussion both have the disadvantage of a high sodium chloride content seven times that of salt poor human albumin

Acacia —This is an inert water soluble substance of high molecular weight The osmotic pressure of a 6 per cent solution is said to approximate that of serum protein according to Saslow[353] the osmotic pressure of such acacia solution being 240 to 260 mm of H_2O and of human serum 376 mm of H_2O It is its high osmotic pressure that suggested its use in the treatment of edema due to decreased osmotic pressure of the blood If injected slowly into the circulation and in not too large amount it has a replacement value for the hypoproteinemia and causes slight or no reactions Another valuable property is its slow disappearance from the blood 40 per cent is said to remain at the end of 7 days and some for a very long period 100 mgm per 100 c c of serum having been found present 1 year 25 mgm 3 years and 10 mgm 6 years after the last injection according to Power Keith and Wakefield[354] Acacia treatment is described with follow up results on 72 patients known to be alive from 2 to 7 years after receiving the drug by Smalley

and Binger[336] of the Mayo Clinic in a very interesting paper from which I will quote

Our plan of treatment is directed toward removing the edema and helping to restore the normal concentration of serum protein Dietary aids consist in restriction of intake of sodium and protection of the normal concentration of serum protein Patients are instructed to take either a salt free diet or one containing only the salt used in preparation of the food Intake of fluids is limited to not more than 1 to 1½ quarts (approximately 1 to 1 5 liters) daily The protein content of the diet is increased to between 75 and 125 gm daily because of the excessive proteinuria that is one feature of the nephrotic syndrome There is no evidence that forced injection of protein produces a significant rise in the concentration of serum protein although it may prevent progress of hypoproteinemia Vitamins and iron may be used to supplement the diet Potassium nitrate is used indefinitely in a dose of 3 gm three times daily This diuretic drug has low toxicity is easily administered and has the desired diuretic action Administration of acacia is indicated, when renal function is good, the concentration of serum protein is low and the edema does not respond readily to treatment in the hospital The usual total dose is 90 gm that is a 6 per cent solution of pure acacia in 1 500 c c of a 0 06 per cent solution of sodium chloride One third of this quantity is given in each of three intravenous injections administered usually on alternate days In the average case in which the intake of fluid is controlled this quantity will give a concentration of approximately 2 gm of acacia per hundred cubic centimeters of blood serum If it fails to give this concentration or if clinical edema is still present, further injection can be given Mercurial diuretic drugs may be more effective after administration of acacia than before

We now propose to discuss certain manifestations of this disease, found at the initial examination and either at reexamination or at the time of the follow up inquiry of the 72 living patients

Of this number at the time of the follow up investigation 49 were doing a full day s work — substantial work as business executives stenographers farmers housewives and students One woman was teaching school in addition to caring for her house and family Two patients were only slightly handicapped 19 were working part time at least half a day and 2 were bed patients One of the latter was a man 74 years of age

'Administration of acacia was instituted 103 times with reference to these 72 patients and 342 separate injections were given Most patients received 90 gm of acacia distributed in 3 injections however 1 patient has received 19 injections, or 5,0 gm, and 12 have received more than 200 gm No ill effects have been reported

The normal concentration of serum proteins is 6 to 8 gm per hundred cubic centimeters and the normal albumin globulin ratio 1 5 to 3 0/1 Among 38 patients reexamined after administration of acacia on a previous visit the value for total serum proteins of 30 was found to have increased In addition the albumin globulin ratio of 2 had become normal Clinically 15 patients of this group of 38 had had ascites or demonstrable pleural fluid in addition to the peripheral edema at the time of the first admission but not at reexamination Also 33 of the 38 patients had no edema or minimal edema of the ankles only at the last admission while all of them had exhibited considerably more edema than this when first seen at the clinic

In 47 of 60 patients with elevated blood cholesterol before acacia was given decrease ensued following this treatment In these patients high cholesterol values were in patients with low serum protein These authors Smalley and Binger[356] believe that the initial amount of blood cholesterol in these patients with Bright s disease has very little prognostic value a view which accords with my own

In 10 of 26 patients with urea retention this returned to normal subsequent to acacia injections In a few patients a previous anemia decreased after the acacia regime Eye ground changes and hypertension with few exceptions were not influenced as would be expected since both of these are features of a renal process progressing into non-edematous Bright s disease which is the usual progression in patients beginning as the edematous type of Bright s disease and not recovering during the earlier phase of the disease This same thing applies too to urea retention and anemia in the majority of such patients

Smalley and Binger[356] end their paper with this statement

This follow up study indicates that many of the patients who had resistant nephrotic edema and who were treated successfully with acacia and other treatments discussed have been able to maintain a more nearly normal economic and social existence than they had been able to lead before treatment As was said in an earlier paragraph we could not find any evidence that acacia was harmful in any way to these patients

When first tried very severe reactions some fatal followed acacia apparently because too much of an impure product was given too fast Now pure acacia is available and if injection is given slowly and stopped at once when a reaction begins it appears to be safe and seems to be the most effective way available at present to control the persisting edema of hypoproteinemia which is very disturbing to the patient and which has failed to respond to high protein diet restricted fluid and salt intake and the use of diuretics

Against the use of acacia apart from the acute reactions due to impurities which no longer occur with acacia now available it has been argued that acacia remains deposited in body cells especially in those of the liver to a less extent in spleen cells and still less in kidney cells and is injurious and that it lowers the level of plasma protein Clinical studies already described do not indicate that such injurious effects appear Such lowering of plasma protein level as occurs seems due to increase in blood volume and not to liver damage the lowering gradually disappears In animals Smalley and his associates[408] have given to dogs large amounts of acacia and followed them subsequently with repeated direct observations of liver and spleen and histological study of liver spleen and kidneys They find that the liver enlarged that cells in all of these organs showed vacuolation presumably due to acacia deposit and that varying amounts of acacia were present in these organs However liver function tests and other tests showed no

evidence of important damage, and they conclude that these results 'do not contraindicate the use of acacia therapeutically under careful management"

Also they have studied patients who had received acacia at varying times before death with these results "In all such cases, in spite of the considerable clinical quantities of acacia that had been administered, the livers were approximately of normal size, the surfaces were smooth, and the tissue was of normal consistency Microscopic sections from these livers did not reveal the inner zonal and periportal lightly and clearly staining areas that were seen in the liver of the animals The cytoplasm of the parenchymal cells contained few large vacuoles and the stain was positive for fat Acacia may have been present, but its presence was not definite The spleen and kidneys appeared normal"

Johnson and Newman[401] in clinical studies also fail to find evidence of toxicity, saying No evidence was found to indicate that the injected acacia inhibited regeneration of plasma protein No serious complications were observed

In view of the clinical and pathological results cited in preceding paragraphs it seems safe to use acacia in the treatment of patients with severe and otherwise uncontrollable edema due to Bright's disease At present this seems the most effective and reasonably economically practical, therapeutic procedure which is available In some patients good diuresis ensues while in others a mercurial diuretic is needed in addition to the acacia In these patients after the acacia the mercurial is effective, when prior to acacia injection its effect has been very slight[401]

Globin from Human Erythrocytes — Such globin is reported[444 445] to be effective in producing a diuresis decreasing edema and increasing plasma protein in chronic edematous Bright's disease (chronic glomerulonephritis) The globin was given intravenously as a 4 per cent solution in normal saline in a dose of 60 gm daily for 6 days No toxic effects were reported This has the further advantage of cheapness as it was prepared from erythrocytes left over from the preparation of plasma Additional reports are needed before forming conclusions as to the value of human globin in the treatment of edema of renal origin

Diuretic Drugs — Often in these edematous patients a considerable to marked diuresis with corresponding fall in body weight and lessening of the edema will follow the use of diuretic drugs using this term to distinguish them from substances used to increase plasma osmotic pressure substances described in the preceding paragraphs The ones that are effective are the acid forming salts ammonium and calcium chloride and ammonium nitrate, urea and the mercurials of which mersalyl mercupurin mercuhydrin and mercurophyllin, are the most satisfactory, these diuretics are usually effective in degree in the order in which the chief groups have been named The xanthine diuretics such as theobromine sodium salycylate (diuretin) or acetate (agurin) or theobromine calcium salycylate (theocalcin) and theophyllin (theocin), as a rule, are not effective When

water and salt restriction and high protein diet fail to decrease edema the following diuretics should be used

The *ammonium salts* are to be given over long periods of time in doses of 5 to 10 gm, 3 to 5 times a day or in smaller doses 5 times a day They should be given in enteric coated tablets or capsules Of these ammonium nitrate seems to produce a minimum of gastrointestinal disturbance occasionally it will cause methemoglobinemia recognized by the development of cyanosis this does little harm and disappears quickly when the drug is stopped

Urea should be given in large amount o to 30 gm 2 to 5 times daily in iced fruit juice or syrup of acacia to mask its taste Some patients find it almost impossible to take urea while others do not appear to mind

The *mercurial diuretics* are given preferably intravenously 2 c c dose at 3 or 4-day intervals it is well to test sensitivity by a preliminary dose of $\frac{1}{2}$ c c At present the preparations generally used contain both mercury and a xanthine usually theophyllin If intravenous injection is not possible they may be given intramuscularly in the same dosage Also they have been prepared in suppository form for rectal use when so used diuresis is apt to be considerably less than when given intravenously or intramuscularly Oral dosage also in the form of enteric coated tablets is effective in some patients and is worthy of trial[1 0] Often better diuresis is obtained if an acid forming salt is given for 2 days before the mercurial diuretic is used Observations of Lyons and his associates[46] indicate that this may be due to a difference in the action of the two types of diuretics the ammonium chloride affecting both extracellular and intracellular fluid compartments while the mercurials remove almost only extracellular fluid

In this type of patient the effect of diuretics is uncertain sometimes an excellent diuresis results in other patients very little increase of urine output occurs and sometimes none In some they are effective only after acacia injections[101] All of these diuretics are safe in patients with the edematous type of Bright s disease, unless as is unusual there is considerable nitrogen retention In a rare patient death may follow the intravenous use of a mercurial diuretic[45, 460] With the mercurials a febrile reaction at times follows intravenous use usually this is mild and should not prevent the use of mercurial diuretics It may follow one injection and be absent after the next Symptoms of mercurial poisoning namely stomatitis colitis hematuria and circulatory collapse do not occur from these mercurials unless nitrogen retention which is unusual in these patients is present to indicate decreased renal excretory activity other than of salt and water or unless there is marked circulatory failure which of course is not present except when there is complicating heart disease with congestive failure If either of these conditions exists these mercurials are to be given very cautiously or not at all With cardiac congestive failure digitalis treatment should precede their use until the circulatory failure has been decreased greatly

evidence of important damage, and they conclude that these results "do not contraindicate the use of acacia therapeutically under careful management"

Also they have studied patients who had received acacia at varying times before death with these results "In all such cases, in spite of the considerable clinical quantities of acacia that had been administered the livers were approximately of normal size the surfaces were smooth, and the tissue was of normal consistency Microscopic sections from these livers did not reveal the inner zonal and periportal lightly and clearly staining areas that were seen in the liver of the animals The cytoplasm of the parenchymal cells contained few large vacuoles, and the stain was positive for fat Acacia may have been present, but its presence was not definite The spleen and kidneys appeared normal"

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SUBACUTE AND CHRONIC HEMORRHAGIC BRIGHT'S DISEASE

Introduction

This is a type of Bright's disease which is characterized by a continued slight to moderate hematuria with at times very little other evidence of a renal lesion This is so predominatingly the feature of the case and so strikingly different from the usual features of Bright's disease as to justify grouping these patients as a special type of Bright's disease Hematuria is usual in acute Bright's disease and it may for a few weeks be a chief feature but this is quite different from the long continued hematuria which characterizes this type of Bright's disease

Etiology and Pathology

In our cases acute infections with a probable high incidence of streptococci as their cause usually have preceded the development of the Bright's disease In the two cases in which we have had the opportunity to study the lesions (these case are described in this section as illustrative cases) the most important le ion has been in the glomeruli which showed increased lobulation and thickening of the capsule or proliferation of the capsular epithelium or were atrophied Hemorrhage was in evidence in many Thromboses of afferent capillaries of glomeruli were not infrequent The epithelium lining tubules may show atrophy but there was little evidence of active degeneration Interstitial tissue was increased in bands separating areas with little or no connective tissue increase The atrophic changes and the connective tissue increase supposedly will be most in evidence in the cases fatal after long duration

Illustrative Cases

The following cases which we have had opportunity to study at the Peter Bent Brigham Hospital exemplify many of the important clinical features of subacute and chronic hemorrhagic Bright's disease

Case XIII — A male age 23 years I B B H Med No 15371 was first admitted to the hospital on February 3 1921 On April 21 1921 he was transferred to the surgical service for operation transferred to the medical service May 5 1921 and was discharged from the hospital May 27 1921 He was readmitted to the medical service March 6 1922 and discharged March 12 1922

His illness apparently began in 1919 at the age of 21 after an attack of influenza which lasted one month At that time he developed pain in the small of the back hematuria polyuria and nocturia He stayed in a hospital for three months with only slight improvement at discharge From then until the patient's first admission to the

Thyroid Gland Substance — Since basal metabolic rate is markedly decreased in many of the patients with the edematous type of Bright's disease, giving thyroid gland substance has been practiced very generally. Response from it, as a rule, does not occur. Since rarely thyroid medication does help, it may be tried. These patients tolerate large doses, far in excess of those effective in true myxedema and so if it is to be used on trial, dosage should be increased rapidly from that appropriate for myxedema to large ones. Often these patients will tolerate enormous amounts before showing the usual signs of thyroid intoxication, there are records of patients having tolerated up to 3.5 gm (50 gr) of dried thyroid daily for days before showing nervousness, tachycardia or any other evidence of thyroid overdosage. The author has never seen any benefit follow giving thyroid to these patients but can see no harm in trying it, he would prefer to stop the trial when without benefit the dose has reached 0.6 gm (gr 10) three times a day. In these patients it is not a failure of absorption of thyroid substance that causes this lack of effect, for these patients also have tolerated well large parenteral doses of thyroxin.

Penicillin — If there is evidence of infection, it seems wise to give penicillin intravenously, if edema is marked, otherwise intramuscularly, at 4 hour intervals, 10 000 to 15 000 units each time. One author[438] reports striking improvement after penicillin in a group of patients with severe acute Bright's disease having some of the clinical features of this form of Bright's disease. In a syphilitic patient with the edematous form of Bright's disease penicillin should be given in large doses at once, dramatic clearing has been reported from it[448, 451] as is discussed in greater detail later on in the section headed, Syphilitic Nephritis.

TABLE X

Urine Examinations and Tests of Renal Function Case XIII

Date	24 Hr Vol	Spr G	Alb	Casts Hy	Casts G an	Casts C W	I I C	II B C	Hb	B U N	Bl Cl	Wt
1921												
Feb 11	SS	1014	++	o	+	o	++++	++				690
Feb 12	SS			+	o	o	++++	+	35	320		690
Mar 14									30	360		660
Mar 15	SS	1010	+	++	+++	+++	+++	+				660
Apr 1	SS	1012	++	++++	+	+++	+++	+	30	330	(op	660
Apr 22	SS	1014	++	++	++	o	+++	++	30	410	6op	650
May 12									20	290	50	620
May 23									24 r	230		620
May 24	SS	1012	+	++	++	+	++++	+				630
Jun 4	SS	1010	++	+	o	o	++	++	33	o		
July 5	SS		++	o	+	o	+++	+				
Aug 17	SS	1 00	++	o	o	o	++++	+	54			718
Sept 21	1600	1005	++	+	o	o	++	+				
Oct 10	SS	1008	++	o	o	o	++	+				
Nov 2	SS	1016	+	o	o	o	+++	+				
Nov 3									44	270	56	
Nov 17	SS	1008	++	+	o	o	++++	+				
Dec 7	SS	1008	++	+	o	o	+++	+				
Dec 28	SS	1009	+	+	o	o	++	+				
1922												
Jan 4	SS		++	+	o	o	+++	+	41	320	5(	
Feb 20	SS	1011	++	+	o	+	++++	+	31	2(0	5(	
Mar 10	SS	1013	+++	++++	++	++x	++++	+				50
Mar 22	SS	1010	+	o	o	o	++	+		320		
Apr 28	SS	1012	++	+	o	+	++	+				
May 18	SS	1008	++	+	+	o	+++	+				
Jun 10	SS	1001	++	+	+	+	+++	+	35	250		750

Peter Bent Brigham Hospital his condition remained practically the same with hematuria more or less constant and much listlessness and weakness During 1920 he continued to have hematuria at times although he improved somewhat He entered the Peter Bent Brigham Hospital to see if the hematuria could be stopped Physical examination at entrance was essentially negative with the exception of the urinary findings

His course in the hospital was marked by a continuation of the bleeding from the kidneys in spite of 78 days of rest and limited diet During his stay physical examination remained unchanged but the renal function became poorer At discharge the phthalein excretion was 18 per cent and the urea nitrogen was 56 mgm per 100 c c of blood (see Table X for urine examinations and tests of renal function) The blood pressure remained normal The blood count dropped moderately and rose again before discharge to approximately the same level as at entrance In view of the predominance of red cells in the urine it was thought that the patient might have a non nephritic source for bleeding Cystoscopic examination and x ray of the kidneys with cultures of urine obtained by urethral catheter revealed no evidence of stone or of any disease other than a bilateral nephritis as responsible for the hematuria

On April 4 the patient was given a transfusion of 550 c c of citrated blood in an attempt to stop the bleeding and to improve his red count which had fallen to 3 664 000 Hematuria actually increased after this procedure but the blood count did improve moderately On April 21 1921 he was discharged to the surgical service for decapsulation of both kidneys In the foreign literature several authors had referred to this procedure as a curative agent for hemorrhagic nephritis At operation the kidneys were quite smooth and not adherent to the capsules There seemed to be no good reason to expect an improvement from stripping of the capsules, but in view of the claims in the literature decapsulation was done A small piece of tissue was removed from each kidney for bacteriological and pathological examination No bacteria were found Histologically the sections showed intracapillary glomerular nephritis both acute and chronic

Immediately after operation there was a marked falling off in the renal function a evidenced by the increase in the blood urea nitrogen from 56 to 90 mgm The patient was discharged back to the medical service on May 5 1921 Here he stayed until May 27 1921 when he was discharged home His course during this period on the medical service was uneventful with the exception of a definite improvement in his renal function and general condition The red count fell off to a low level of 2 368 000 with a hemoglobin of 52 The urine continued to show much microscopic blood

Following discharge from the hospital he was seen frequently in the Outdoor Department He rested a large part of the time at home and adhered fairly well to the low protein salt poor diet The urine however continued to show numerous red blood cells and a few casts With an increase of activity or with a mild infection there was an increase in the number of red blood cells in the urine for a few days The phthalein excretion was 54 per cent and the blood urea nitrogen 22 mgm two months after discharge However the tendency was for the phthalein output to decrease and the blood urea nitrogen was constantly above normal

On March 6, 1922 the patient entered the Peter Bent Brigham Hospital for the third time because of increase in the number of the red cells in the urine He was discharged

I LOOD PRESSURE CASE XIII

Date	*Systolic*	*Diastolic*
Feb 4 1921	130	75
Mar 1	132	90
Apr 1	132	80
May 2	130	8
June 4	128	80
July 8	128	82
Aug 17	128	82
Sept. 7	144	88
Oct 10	140	90
Nov 2	150	90
Dec 12	146	100
Jan 4 1922	148	90
Feb 1	132	78
Mar 6	144	86
Apr 0	146	90
May 18	132	88
June 3	144	89
July 1	134	93
Aug 19	138	82
Sept 16	144	94
Oct 7	138	82
Nov 4,	132	92
Dec 23	142	98
Jan 25 1923	154	110
Feb 26	48	87
Mar 27	158	98
May 3	148	100
Sept 28	1 2	128
	154	122
Jan 28 1924	182	108

on March 12 1922 This flareup in his kidney condition was apparently due to a cold and the hematuria quieted down again in a few days The course in the hospital in this admission was otherwise uneventful

During the re t of the year 1922 the patient was seen frequently in the Outdoor Department His only complaint was nervousness and a rare headache The outstanding feature of the case was the continuation of microscopic bleeding from the kidney with the finding of only a few ca ts some of which were of the red blood cell variety The red cells varied greatly in number the increa e usually being associated with an acute infection or increased physical exertion The phthalein output varied from 38 per cent to 60 per cent and the blood urea nitrogen from 35 to 27 mgm At the end of 1922 the red blood cell count had fallen to 2 980 000 The blood pressure at times rose slightly above normal but usually was within normal limits Retinal examination was negative The patient was seen occasionally during the year 1923 His complaints were those of nervousness pallor rare headache with nausea and vomiting

TABLE X (Cont)

URINE EXAMINATION AND TESTS OF RENAL FUNCTION CASE XIII

Date	4 Hr Amt	Sp Gr	Alb	Casts Hy	Casts Gran	Casts Cell	R B C	W B C	Ph	B U N	Bl Cl	Wt
1922												
July 8	S S	1 009	++	+	+	+	++++	+	39	35 0		
July 22	S S	1 005	++	++	o	o	++	+	35 %	27 0		
Aug 26	S S	1 010	++	+x	o	o	+++	+	45 %	31 0	5 63	
Sept 16	S S	1 006	++	+	o	+	+++++	+				
Sept 23	S S	1 008	++	o	o	o	+++	+				
Oct 7	S S	1 008	++	+x	o	o	+++	+				74 6
Nov 4	S S	1 007	++	+	+	o	+++	+	60 %	28 0	5 48	
Dec 23	S S	1 009	++	+	+	o	+++	+				
1923												
Jan 25	S S	1 008	++	+	+	+	+++	+	28 %	32 0	5 29	
Jan 29	1 100+	1 009	++	+	o	+	+++	+				
Feb 26	S S	1 006	++	+	+	+	++++	+				
Mar 27	S S	1 006	++	+	+	o	+++	+				77 4
May 3	S S	1 010	++	+x	+	o	+++++	+	24 %	27 0	5 54	
May 28	S S	1 010	++	o	+	o	++++	+				
Sept. 28	S S	1 010	++	+x	+	o	+++++	+	20 %	32 0	5 54	78 8
1924												
Jan 28	S S	1 010	++	+	+	+	+++	+	15 %	45 0	4 89	

Sp Gr = Specific gravity Alb = Albumin Hy = Hyaline Gran = Granular Cell = Cellular R B C = Red blood cells W B C = White blood cells Ph = Phenolsulfonephthalein excretion in two hours B U N = Blood urea nitrogen in milligrams per 100 c c of blood Bl Cl = Blood chloride in grams per liter of blood Wt = Weight in kilos

* S S = Single specimen
\+ = Very slight trace of albumin
++ = Slight trace of albumin
+++ = Much albumin
++++ = Very much albumin

** + = Rare
++ = Numerous
+++ = Many
++++ = Very many
+++++ = Very very many
p = Plasma
x = Red blood cell cast
= With fat

until January 1924 when the high level of 182 mm systolic and 108 mm diastolic was noted The renal function at all times has been somewhat decreased but has fluctuated moderately The later observations showed a very definite reduction in function He died on Dec 8 1925 6 years after onset of the disease and autopsy showed chronic glomerulonephritis The cause of death was pneumonia not Bright s disease although the latter was a contributory cause in all probability

Case XII — A male age 34 years entered the medical service of the hospital for the first time on December 15 1919 Med No 12 515 and was discharged February 27 1920 Subsequently he was in the hospital from November 8 1920 to January 15 1921 from October 5 1921 to October 20 1921 and from March 2 1922 to April 4 1922 when he died about 6 years after onset of the Bright s disease

At the first admission the patient gave a history of severe tonsillitis with what seemed like an acute Bright s disease following it in 1916 3 years before the time of admission A year later (1917) the patient had shortness of breath and at that time albumin was found in his urine He was discharged from the army in that year with the diagnosis of nephritis In August 1919 the patient began to have severe unilateral headaches with nausea and vomiting These suggested migraine He consulted his physician for relief from these headaches and he found considerable albumin in his urine and diagnosed the condition as uremia At entrance into the Peter Bent Brigham Hospital the physical examination was negative with the exception of slightly palpable radial arteries a heart that was somewhat enlarged and a blood pressure of 150 mm Hg systolic and 100 mgm diastolic (Table XII) The urine showed the typical picture of an active nephritis with considerable albumin numerous casts and red blood cells The renal function was somewhat depressed with a phthalein excretion of 30 per cent and a urea nitrogen of 28 mgm per 100 c c of blood (see Table XI)

The patient stayed 73 days in the hospital during which time he had no symptoms referable to his kidneys. The urine continued however to show blood and at times it was scanty in amount Before discharge the red cells in the urine had decreased very materially The blood pressure which at entrance was elevated dropped to a normal level Anemia was slight On one occasion only did the red cells go below 4 000 000 The hemoglobin fluctuated from 70 per cent to 80 per cent

After his discharge from the hospital he was followed in the Outdoor Department He continued to show more or less blood in his urine with only an occasional cast About the middle of July 1920 casts began to be more numerous the blood increased the blood pressure (Table XII) slowly climbed from 126 mm Hg systolic and *78 mm diastolic to 190 mm Hg systolic and 100 mm diastolic* It reached this last figure on October 19th Owing to the increase in the number of red cells and casts and to the increase in blood pressure the patient was sent into the hospital on November 8 1920 to see if a more carefully controlled diet and rest would cause a reduction in the hematuria and blood pressure Examination at this time showed a slightly enlarged heart with a blowing systolic murmur at the apex and palpable peripheral arteries The blood pressure was 170 mm Hg systolic and 100 mm diastolic. The urine contained many hyaline casts and very numerous red blood cells The phthalein excretion had fallen off to 23 per cent and the urea nitrogen had reached the level of

and occasional unexplained attacks of crampy pain in the abdomen The urine continued unchanged The phthalein excretion fell off to a low level of 20 per cent The blood urea nitrogen remained fairly low ranging from 27 to 32 mgm The blood pressure generally was above normal The heart showed an occasional extrasystole and a presystolic gallop rhythm At times there was slight pitting edema of the shins Retinal examination showed slight arteriosclerosis and a few spots of degeneration The patient was seen in January 1924 at which time he was apparently in very good health Hematuria however persisted the phthalein excretion had fallen materially to 15 per cent, and the blood urea nitrogen had risen to 45 mgm The blood pressure was 182 mm systolic and 108 mm diastolic

In Dec 1925 the patient developed pneumonia went to the Boston City Hospital, died on Dec 8 1925 and was autopsied

Autopsy — Diagnoses nephritis chronic glomerular pneumonia, lobar, hypertrophy of heart arteriosclerosis early *Heart* weighed 525 gm otherwise it seemed normal *Lungs* showed extensive lobar pneumonia in stages of gray and of red hepatization *Kidneys* combined weight 250 gm had thickened capsule stripping with difficulty to leave a granular surface Cortex measured 0 6 to 0 8 cm Pelves and ureters were normal Microscopic examination of kidneys showed the following Some of the convoluted tubules are dilated others are atrophic Some of the tubules contain granular casts other casts resembling hemoglobin casts Many of the glomeruli are completely sclerosed and hyalinized Others show increased number of nuclei and adhesions between the tuft and capsule An occasional glomerulus shows hemorrhagic infarction A few glomeruli show no changes There is intimal thickening of the arteries and a marked degree of hyperplastic arteriolosclerosis There is a diffuse increase in the interstitial connective tissue which shows a focal infiltration of lymphocytes

Summary of Case XIII — A young man of 23 years of age entered the Peter Bent Brigham Hospital 2 years after the development of a hemorrhagic Bright's disease following influenza The bleeding from the kidneys continued for practically 6 years with only slight variation in amount the increase often being associated with acute infections or excessive physical exertion The bleeding was proved to be associated with his nephritis by the exclusion of renal stone or other non nephritic causes by the constant finding of casts and by the study of kidney tissue obtained at operation The bleeding obviously was mechanical and not due to chemical or other known changes in the character of the blood The hematuria persisted in spite of prolonged rest in bed with a diet low in protein, salt and fluid The number of the red cells in the urine, however, increased when the patient was allowed to undertake any physical exertion There was no improvement noted after transfusion or after decapsulation of the kidneys In spite of the prolonged bleeding marked anemia has not been a constant feature There has been a reduction to the low level of 2 368 000 with a hemoglobin of 52 per cent, but this steadily improved until the red count was practically normal The last observation showed a fairly definite falling off in the number of red cells in the urine The blood pressure at first was normal but has risen very slowly

TABLE XI (Cont)

URINE EXAMINATIONS AND TESTS OF RENAL FUNCTION CASE XIV

Date	24 Hr Am	Sp G	Alb	Cast Hy	Cast Gran	Cast Cell	R B C	W B C	Ph	B U N	Bl Cl	Wt
1921												
July 20	1 750	1 005	++	0	0	0	+++	+				68 0
Aug 3	2 500	1 010	++	+	0	0	++	+	22 0	42 0	4 84	68 0
Sept 14	S S	1 012	++	+	0	0	++++	+				67 0
Oct 3	S S	1 008	++	+	0	0	++++	0	18	55 0	4 39	
Oct 18	S S	1 012	++	0	0	0	++	0	17 0	49 0	4 29	
Nov 9	2 250	1 005	++	0	+	0	++++	+	13 0	46 0	4 93	66 4
Dec 14	2 2 0	1 010	++	+	+	0	++x	+				64 9
1922												
Jan 5	2 000	1 016	+	0	0	0	++x	+	9	55 0	4 88	
Jan 28	2 000	1 005	++	+	0	0	++	+	6	55 0		
Feb 18	0 0	1 004	++	+	+	0	++++	+				65 6
Mar 3	1 750	1 018	++	0	+	0	++++	+				
Mar 11	S S	1 008	++	0	+	0	++++	+	tr	88 0		
Mar 17	1 900	1 008	++	+	+	0	++++	+				
Mar 24	S S	1 012	+++	0	0	0	++++	+	tr	1 24	3 45	62 2
Mar 30	S S	1 014	++	0	0	+	++++	+		2 11	3 45	61 8
Apr 3		1 012	++++	0	0	0	+	+		266 0	3 45	
Apr 4	Died											

Sp Gr = Specific gravity Alb = Albumin Hy = Hyaline Gran = Granular Cell = Cellular R B C = Red blood cells W B C = White blood cell Ph = Phenolsulfonephthalein excretion in two hours B U N = Blood urea nitrogen in milligram per 100 c c of blood Bl Cl = Blood chlorid in grams per liter of blood Wt = Weight in kilos

† S S = Single specimen
\+ = Very slight trace of albumin
++ = Slight trace of albumin
+++ = Much albumin
++++ = Very much albumin

*
\+ = Rare
++ = Numerous
+++ = Many
++++ = Very many
+++++ = Very very many
p = Plasma
x = Rare red blood cell cast
xx = Numerous red blood cell casts
xxx = Many red blood cell casts

TABLE XI

URINE EXAMINATIONS AND TESTS OF RENAL FUNCTION CASE XIV

Date	4 Hr Amt	Sp Gr	Alb	Casts Hy	Casts Gran	Casts Cell	R B C	W B C	P h	B U N	Bl Cl	Wt
1919			*	*	**		*					
Dec 15	S S†	1 014	++++	+++	+++	o	+++	o	30' c			62 8
Dec 27	S S	1 015	+++	o	+++	o	+++x	o				61 8
1920												
Jan 5									40 o	25 0		61 0
Jan 16	S S	1 010	++++	+++	+++	o	+	o				60 2
Feb 1	S S	1 015	++	o	+	o	+	o				60 6
Feb 2									45' o	25 0		
Mar 31	2 500	1 004	+	o	o	+	+++	**+				
Apr 21	S S	1 00?	+	+	o	o	+	+				69 8
May 17	1 750	1 010	+	o	o	o	++++	+	39 c	12 0	4 63	,00
June 9	S S	1 005	++	+	+	o	+++	+				70 0
July 17	1 500	1 010	++	++	+	+	++++	+				68 5
Aug 19	1 750	1 012	++	o	o	o	++	+				
Sept 29	1 750	1 008	++	++	++	o	+++++	+	30	29 0	6 31p	68 4
Oct 19	1 750	1 010	++	o	+	o	++++	+				
Nov 22	S S	1 014	+++	+	o	o	+++++	+	?	39 0		63 0
Dec 11	S S	1 010	++	o	o	o	+++++x	+				64 0
Dec 18	S S	1 012	+++	o	o	o	+++++xxx	+				64 0
Dec 21	S S	1 010	++	+	o	o	+++++xx	+				64 0
Dec 29	S S	1 014	++	+	o	o	+++x	+				63 8
Dec 31	S S	1 012	++	+	+	o	+	+				64 0
1921												
Jan 4	S S	1 014	++	o	+	o	++++x	+				
Jan 19	S S	1 011	++	++	++	o	+++x	o				63 4
Feb 16	S S	1 006	++	o	o	o	+++	++				67 5
Mar 30	1 750	1 011	++	+	o	o	++++	+				69 0
Apr 21	S S	1 008	++	o	o	o	+++	+	21	29 0	5 35	68 0
May 4	S S	1 00?	++	+	o	o	+	+				68 5
June 2	S S		++	o	[illegible]	o	+++	+	30	4 0	4 86	67 2

TABLE XI (Cont)

URINE EXAMINATIONS AND TEST OF RENAL FUNCTION CASE XIV

Date	24 Hr Vol ml	Sp Gr	Alb	Casts			R B C	W B C	Ph	B U N	Bl Cl	Wt
				Hy	Gran	Cell						
1921												
July 20	1 750	1 005	++	o	o	o	+++	+				68 0
Aug 3	2 500	1 010	++	+	o	o	++	+	22 0	42 0	4 84	68 0
Sept 14	S S	1 012	++	+	o	o	++++	+				67 0
Oct 3	S S	1 008	++	+	o	o	++++	o	18	55 0	4 39	
Oct 18	S S	1 012	++	o	o	o	++	o	17	49 0	4 29	
Nov 9	2 250	1 005	++	o	+	o	++++	+	13	46 0	4 93	66 4
Dec 14	2 250	1 010	++	+	+	o	++x	+				64 9
1922												
Jan 5	2 000	1 016	+	o	o	o	++x	+	9	55 0	4 88	
Jan 28	2 000	1 008	++	+	o	o	++	+	8 0	55 0		
Feb 18	2 000	1 004	++	+	+	o	++++	+				65 6
Mar 3	1 750	1 018	++	o	+	o	++++	+				
Mar 11	S S	1 008	++	o	+	o	++++	+	tr	88 0		
Mar 17	1 900	1 008	++	+	+	o	++++	+				
Mar 24	S S	1 012	+++	o	o	o	++++	+	tr	1 24	3 45	62 2
Mar 30	S S	1 014	++	o	o	+	++++	+		2 11	3 45	61 8
Apr 3		1 012	++++	o	o	o	+	+		266 0	3 45	
Apr 4	Died											

Sp Gr = Specific gravity Alb = Albumin Hy = Hyaline Gran = Granular Cell = Cellular R B C = Red blood cells W B C = White blood cell Ph = Phenolsulfonephthalein excretion in two hours B U N = Blood urea nitrogen in milligrams per 100 c c of blood Bl Cl = Blood chlorid in grams per liter of blood Wt = Weight in kilos

†S S = Single specimen
+ = Very slight trace of albumin
++ = Slight trace of albumin
+++ = Much albumin
++++ = Very much albumin

+ = Rare
++ = Numerous
+++ = Many
++++ = Very many
+++++ = Very very many
p = Plasma
x = Rare red blood cell casts
xx = Numerous red blood cell casts
xxx = Many red blood cell casts

TABLE XII

Blood Pressure, Case XIV

Date		*Systolic*	*Diastolic*
Dec 15 1919		170	100
Feb 17 1920		126	78
Mar 10		160	88
Apr 21		1,4	96
May 17		176	98
June 24		190	98
July 17		1,0	100
Aug 19		1,4	100
Sept 29		190	100
Oct 19		17	86
Nov 18		157	102
Dec 18		180	105
Jan 19 1921		208	118
Feb 19		210	108
Mar 16		196	104
Mar 25		194	102
June 29		200	100
July 20		198	118
Aug 1,		184	110
Sept 14		220	110
Oct 20		180	110
Nov 23		214	110
Dec 14		222	118
Jan 21 1922		196	112
Feb 18		198	112
Mar 27		232	130
Apr 3		170	86
Apr 4	Died	148	,8

Blood Counts Case XIV

Date	*W B C*	*R B C*	*Hemoglobin*
Dec 15 1919			70 %
Nov 9 1920		4 312 000	80%
27	, 00	3 488 000	70%
29	8 ,00	4 016 000	80%
Dec 21		4 104 000	
June 2 1921		4 240 000	,0%
Oct 7		4 080 000	76%
10		4 196 000	73%
Nov 23		3 956 000	75%
Mar 4 1922		4 752 000	75%
24		816 000	55%
Apr 3		680 000	50%

Nov 27 1920	Coagulation time 5 min	bleeding time 3 min	platelets 190 000
29	8 min	5	210 000

34 mgm per 100 c c of blood During the patient s stay in the ho pital he was cystoscoped and had x rays of his kidneys and ureters but no stone or other cause of bleeding than nephritis was discovered Coagulation time bleeding time and platelets as well as the calcium in the blood seemed normal On December 22 1920 he was given a transfusion of 500 c c. of citrated blood which caused a well marked increase in the amount of blood cells in the urine The patient stayed in the hospital 69 days during which time the bleeding continued varying in amount The blood pre sure dropped to 155 mm Hg systolic and 95 mm dia tolic before discharge Tests of renal function showed essentially no change

During the interval between the second and third admission he was followed in the Outdoor Department He adhered strictly to low protein diet and limited his exercise to not more than a few hours a day In pite of this his hematuria continued the renal function fell off moderately the phthalein excretion reaching the low level of 17 per cent and the blood urea nitrogen the high level of 55 mgm shortly before the third admission The blood pressure climbed steadily until it reached a high level of 220 mm systolic and 110 mm diastolic in September 1921

On October 5 1921 the patient was admitted to the hospital for the third time for observation because of the falling off of the renal function and the marked increase in blood pressure During this admission the patient stayed only 15 days The hematuria decreased considerably while the patient was resting the renal function changed less The blood pres ure fell to 180 mm systolic and 110 mm diastolic Ophthalmoscopic examination at this time showed a few pin point hemorrhages in both retinae and beginning arteriosclerosis

In the interval between the third and last admission the patient was seen several times in the renal clinic of the Outdoor Department He felt fairly well up to one month before the la t admission except for dull headaches over the temporal region two or three times a week and some dyspnea and palpitation on exertion About a month before coming into the hospital he complained about headaches occurring every morning occasionally persisting all day During the same time he had vomited about once a week but during the last three days he had vomited after every meal During the same month his vi ion began to fall off so that he was unable to read anything except large type Then noises in his ears appeared and increasing deafness For a week there had been twitching in various parts of the body The blood pressure while at home rose to the high level of 232 mm Hg systolic and 124 mm diastolic His urine continued to show an abundance of blood The renal function fell off so that the phthalein excretion was only a trace and the blood urea nitrogen rose to 88 mgm Because of obvious uremia *the patient was sent into the ho pital for treatment*

At this time physical examination howed well marked enlargement of the heart peripheral and retinal arteriosclerosis a blood pressure of 220 mm Hg systolic and 115 mm diastolic urinous breath pallor and marked retinitis During hi stay in the hospital he showed the usual signs and symptoms of marked uremia with severe nausea vomiting itching twitching and drowsiness There was in ad lition marked blee ling from the nose from time to time and Cheyne Stokes re piration develop d A pericardial friction rub was heard on March 28th This continued until the time of death on April 4 1922 He had no convul ions and merely became weaker and weaker The

urine during his stay in the hospital showed an increase in albumin but little change in the red cells until just before death when they became comparatively few The blood pressure showed the usual terminal falling off reaching 148 mm Hg systolic and 78 mm diastolic on the day of death The 'phthalein excretion had remained a trace, and the blood urea nitrogen steadily climbed to 266 mgm on the day before the patient died A well marked secondary anemia developed in the last month of the patient s illness (see Table XIV)

Autopsy showed chronic glomerular nephritis hypertrophy and dilation of the heart fibrinous pericarditis healed tuberculosis, fibrous pleuritis, atheroma of the aorta and splenic artery The kidneys were definitely shrunken and small They contained small cysts under each capsule Microscopically the glomeruli showed extensive injury varying from complete sclerosis to hyalinization of a portion of the glomerulus The glomeruli frequently were adherent to Bowman s capsule which showed at times marked proliferation of the epithelium and some of the afferent vessels of the glomeruli were thrombosed Many of the tubules were atrophied and some seemed cystic.

Summary of Case XIV — A young man of 34 entered the hospital in 1919 with a hemorrhagic Bright's disease which dated back to tonsillitis in 1916 From the first admission 3 years after probable onset until his death in 1922 he continued to have observed hematuria and evidences of Bright's disease The bleeding responded to no treatment whatsoever but was worse on exertion The blood pressure steadily rose to a high figure This accompanied a progression in the Bright s disease as indicated by a fairly steady diminution in renal function The patient died in azotemia about 6 years after his Bright's disease began

SYMPTOMATOLOGY AND PHYSICAL FINDINGS

In onset these patients have much the same picture as many of those with acute Bright's disease in which edema is not a prominent feature Unlike other types of acute Bright s disease hematuria persists and is the striking feature of the case This hematuria usually is slight often it might be overlooked, because albumin is slight in amount and unfortunately with so small an amount of albumin the physician may make no microscopic examination of urinary sediment, and a small number of red blood cells, persistently present, are missed

O'Hare has divided the clinical course of this type of nephritis into three stages The first stage usually lasts a few weeks and has the appearance of rather mild acute Bright s disease The second stage is characterized by continuous bleeding without increase in blood pressure and without change in renal function This stage may last as much as a year The second stage gradually merges into the third with decreasing renal function as measured by various tests and increasing blood pressure The second stage cases may and usually do recover the third stage cases progress with a tendency towards uremia at the end, but they may last for years

A very striking thing about these patients is that notwithstanding the hematuria, anemia is long absent or very slight in degree When renal function finally becomes poor, anemia may develop as in a case of chronic Bright s disease of other type

Besides red cells the urine contains a small amount of albumin and an occasional hyaline finely granular or red cell cast The casts may be difficult to find Renal function usually is good in a few cases blood urea nitrogen is high and phthalein excretion low

Blood pressure usually is normal or slightly raised In some of the later stages of progressing cases blood pressure is high Usually there are no circulatory symptoms or lesions

Diagnosis

Diagnosis is most important It depends on finding a few casts especially red cell casts among the red cells and this requires patient careful examination of the sediment Except for the casts the urine is consistent with such causes of hematuria as papilloma of the bladder painless renal calculus hypernephroma a tuberculo is unaccompanied by pus or cystitic symptoms etc It is wise to exclude these by appropriate cystoscopic and x ray examinations if the evidences of Bright s disease are slight because casts may appear in the urine of these other patients by reason of slight accompanying renal changes It is preferable to discommode a patient with probable hemorrhagic Bright s disease by the diagnostic methods of genitourinary surgery rather than to miss a bladder or renal condition that should be operated on

Prognosis

Some of these patients get well although the progress to recovery may be slow Most are long drawn out and many gradually progress downward as a chronic non edematous Bright s disease

Treatment

Treatment is very unsatisfactory General hygienic and dietary methods of managing Bright s disease are applicable There seems no reason for a diet markedly restricted as to any of its constituents Rest in bed prolonged over months is indicated Nothing beyond rest in bed seems to have any definite effect on the bleeding

I have seen tried ergot calcium transfusion of blood vaccines tonsillectomy even renal decapsulation, all to no avail

CHRONIC NON-EDEMATOUS BRIGHT'S DISEASE

Several Modes of Progression to Common Clinical Picture

Under chronic non edematous Bright s disease are grouped patients who have similar symptoms similar physical signs and similar changes in urine and blood at the time they come to the attention of the phy cian as having evidences of a chronic, progressive disease These patients at autopsy, however show in the kidney the pathological lesions of the late or end stages of several fundamentally different pathological processes In other words a differing pathogenesis has resulted in pathological lesions that produce essentially the same clinical picture, when the process has arrived at the stage of chronicity

In some of these patients the process has commenced as an acute Bright's disease of hemorrhagic type as already described under that heading, cases in which with this clinical picture recovery fails to take place, but after an interval there appears the picture of what we term chronic, non edematous Bright's disease There may be a steady progression from the acute to the chronic disease with an intermediate stage combining changes found in each, a stage which can be termed subacute More often after the acute disease subsides, there may be a period short or long of essentially good health but with some persisting evidences of kidney disease, found particularly by study of the urine When the period of good health is long, we speak of this as a period of latency The lesion in the kidney from a patient with this progression into chronic Bright s disease would be called by the pathologist chronic glomerulonephritis

In numerous patients with the later progression as just described in the preceding section the onset has been insidious There has been no recognized acute illness with evidence of acute Bright s disease although there may have been one or several attacks of those acute conditions commonly causative of acute Bright s disease such as scarlet fever tonsillitis or other acute infectious disease with prominence of infection with streptococci The first symptom noted is one of those due to chronic Bright s disease At this time, as a rule, vascular lesions are not prominent although some degree of hypertension is present In some of these patients however vascular lesions come early into prominence When one studies sections of the kidney from such a patient the process is found to be one in which sclerosis and atrophy of glomeruli dominate the picture, sometimes with and sometimes without glomeruli in which still can be made out evidences of an earlier proliferative process either intracapillary or capsular in type or both These kidneys pathologically are like those in patients in whom in the beginning an acute hemorrhagic type of Bright s disease has been observed These patients have pathologically definite or presumptive chronic glomerulonephritis If at

any time in these patients there has been a period of edema albuminuria hypoproteinemia and hypercholesterolemia the probability that the kidney has the lesions of glomerulonephritis is very great[447]

Another group is the one which throughout the course of the disease shows a urine, not grossly bloody but containing in the sediment numerous red blood cells a form of Bright s disease described in the preceding section

In others of these patients very considerably fewer in number than the preceding group the disease has begun as acute or subacute Bright s disease with edema in the terminology preferred by some as nephrosis or the nephrotic syndrome In an occasional patient before the shift to chronic non-edematous Bright s disease takes place the edematous stage has persisted so long as to have justified the term chronic Bright s disease with edema The clinical picture in the edematous stage already has been described under the heading Acute Subacute and Chronic Edematou Bright s Disea e (Nephrotic Type) or Nephrotic Syndrome of Bright s Disease In most of these patients however with continuing illness there is a progressive shift from the edematous to the non-edematous clinical picture as has been described on a previous page under a subheading of Acute Subacute and Chronic Edematous Bright s Disease Clinical Course In some but less frequently than in the group commencing as the hemorrhagic type of acute Bright s disease there is an intermediate stage of apparently good health of varying length but usually there is not a long period of latency In this group of patients after reaching the chronic non-edematous stage the renal lesion pathologically is a chronic glomerulonephritis it is not possible from the pathological appearance of the kidney except in a very rare patient to say whether the disease has begun as acute hemorrhagic type of Bright s di ease or as acute or subacute edematous type (nephrotic syndrome) of Bright s disease Very rarely with a late clinical picture of chronic non-edematous Bright s disease the pathological lesion is only a thickening of the wall of the capillaries of the glomerular tufts to a degree to hinder blood flow through the glomeruli[178] so far as I know this occurs only in patients who have shown the clinical picture of edematous Bright s disease not in those whose disease began as acute hemorrhagic Bright s disease

A much larger group of patients with the symptoms physical signs and changes in urine and blood diagnostic of chronic non edematous Bright s disease have an entirely different renal process There is no recognized acute stage of this form of Bright s disease Instead u ually gradually sometimes rapidly the clinical picture evolves In these patients periods of the nephrotic syndrome have not occurred[447] Evidence of vascular disease dominates the clinical picture in this group sometimes being apparent before there is much clinical evidence of change in renal function sometimes appearin as the renal lesion seems to be developing sometimes seemingly following the developing evidences of kidney disease The pathological lesion in these kidneys is well described by the term

arteriolonephrosclerosis or chronic vascular nephritis, in a few patients by the term arteriolonecrosis of the kidney

A fourth group of patients, not as commonly seen as the preceding group but being recognized now with increasing frequency, has a very different form of progression into a stage with a clinical picture toward the end essentially like that of the other groups here being described, the renal process in these patients has begun as acute or subacute pyelonephritis, in which in healing or with the subsidence of evidences of diffuse bacterial inflammation of the kidney the renal parenchyma has undergone scarring with various secondary or concomitant changes in glomeruli and tubules Pathologically this is a healing or heal d pyelonephritis, a chronic pyelonephritis but clinically it is a chronic non-edematous Bright's disease

Then there are other groups a fifth group of cases of chronic non-edematous Bright's disease relatively small in number and now apparently decreasing in frequency in which the progression into chronic non edematous Bright's disease has taken place via renal amyloidosis a sixth group very small in number indeed, in which the clinical picture results from hypoplasia of the kidney, which may be due to an anomaly of blood supply or be of congenital origin and a seventh group due to polycystic kidney These groups 5 to 7 along with some others are discussed later on under the heading, Certain Special Syndromes of Bright's Disease

Etiology

The etiology in the first and second groups of patients as classified in the preceding section is that already described for acute Bright's disease of hemorrhagic type and for acute subacute and chronic edematous Bright s disease (nephrotic syndrome) under these headings In them infections and infectious diseases especially those due to streptococci dominate the etiology The etiology of the third group those dominated by evidences of vascular disease is very poorly understood as has been pointed out in Part I where various possible causative factors are discussed That this form of chronic non edematous Bright's disease is closely related in cause to chronic vascular disease in general, to other so-called degenerative diseases and to primary hypertension seems very probable, but what in particular causes all of these is unknown at present Heredity is an important factor in etiology but how this works to these ends is not known

The etiology of the fourth group those following acute and chronic pyelonephritis, seems very definite In these bacterial infection frequently combined with some form of inefficient emptying of the urine into the bladder via kidney, pelvis and ureter is the cause A variety of bacteria can function in this way The group of chronic non edematous Bright s disease those with amyloidosis, occur most frequently in patients with advanced tuberculosis especially the

chronic pulmonary form but may follow any form of chronic inflammation such as empyema of the chest, osteomyelitis and also can occur in association with some neoplasms Of interest is the case in which no cause for the amyloidosis *can be found The groups with hypoplasia of the kidney and with polycystic* disease of the kidney can be considered as anomalies of development rather than conditions of acquired disease

Pathology and Pathogenesis

Kidney

The most striking feature of the gross pathology of the kidney in all of this group with the clinical picture of chronic non-edematous Bright s disease except the polycystic kidney is decrease in size These kidneys are smaller than the normal often much smaller reddish or gray in color often having a finely lobulated or granular surface with the capsule more or less adherent so as to bring away bits of renal tissue when it is stripped off On measurement of the cut surface the cortex is thinned frequently to a very marked degree Blood vessels often are prominent and frequently stand open in the freshly cut surface The paler grayish kidneys usually are the ones with lesions described under the pathological terms glomerulonephritis chronic pyelonephritis amyloidosis or hypoplasia the red kidneys as a rule are those considered as having vascular nephritis or arteriolonephrosclerosis The polycystic kidney is larger than normal, often very much so and obviously cystic throughout with cysts varying from *those just visible to fairly large ones all crowded closely together In all of these* kidneys areas of parenchymal hemorrhage are infrequent but in the polycystic kidneys some cysts as a rule contain blood in varying appearance from that of fresh blood to a brownish residual material

The microscopic picture in these kidneys is a varied one Glomeruli practically always and diffusely are changed from normal and these glomerular changes dominate the picture Glomeruli show combinations of cellular proliferation with secondary degeneration and connective tissue proliferation leading to a progressing atrophy of glomeruli and final complete disappearance of many of them (see Figs 17 to 21 in Part I) Many pass through a stage of increasing lobulation to intra and inter-capillary fibrosis and shrinkage The capsule of the glomeruli thickens and fibroses Portions of the glomerular tuft often become attached to the capsule cyst like spaces appear and total capsular space decreases in size and finally often largely disappears The glomerular capillaries show thickening of their walls often with hyaline transformation Many of them become thrombosed Other capillaries arterioles and arteries show similar changes the larger ones having thickened intima often with newly formed elastica inside the old

Some of the change in the larger arteries is considered a compensatory one from the decreased need of the shrunken kidney for blood supply Venules and veins often show changes somewhat similar to those in the arterial system, although these are less marked and less obvious than the changes in the arteries

With these changes in glomeruli and blood vessels go changes in the tubules. In general the more atrophied and sclerosed the glomeruli, the greater the change in the tubules connected with them The epithelium of the tubules, particularly of the convoluted ones, shows various degenerative changes, many of the cells lining tubules atrophy and lose their granularity, some necrose, some change to a low cuboidal type, some to a high columnar type Some tubules dilate and become tortuous Some tubules atrophy completely and disappear this happens especially to tubules connected with glomeruli whose function has ceased by reason of the pathological changes in them Some tubules remain as aglomerular tubules, apparently with some persisting excretory function Some tubules, probably pinched off by closure of their lumens change to small thin walled cysts lined by very flat epithelial cells resembling those lining the capsules of glomeruli Such cysts are not very numerous except in the polycystic kidney of different origin and pathogenesis to be described later

The changes in glomeruli and tubules just described in totality constitute an atrophy of the renal parenchyma, particularly the cortical part of the kidney

While these changes are going on there appears an increase in the interstitial tissue Some of this is only apparent, resulting from a decrease in size and disappearance of glomeruli and tubules bringing the normal interstitial tissue fibrils into closer juxtaposition and so becoming more apparent in the stained sections of the kidney Much of it however, is real, caused by proliferation of connective tissue cells and fibrils Also varying degrees of cell infiltration, chiefly lymphocytes and plasma cells occurs to add bulk to the interstitial tissue There also may be some edema Newly formed connective tissue gradually loses its cellularity, becomes more fibrosed and so shrinks to decrease kidney size further Since scattered groups of glomeruli and attached tubules shrink much while others do not the interstitial tissue where shrinkage is most tends to be grouped into ill defined bands between areas of lessened change in kidney constituents this causes the irregularity of kidney surface and the points of firmer attachment of capsule to kidney

Normal renal circulation passes the bulk of the blood first to and through the glomeruli and thence to the intertubular supportive framework Consequently any process disturbing intraglomerular blood flow secondarily disturbs inter tubular blood flow and tubular nutrition Consequently in kidneys with exten ive glomerular lesions there are resultant degenerative changes in the tubules and proliferative changes in the connective tissue with various lesions in the inter tubular blood vessels The end result there can be much the same, whether the

lesion in the glomeruli is primarily a parenchymal one of the glomerulus or a vascular lesion in the afferent or the efferent vessel to the glomerulus

When the renal lesion dominantly is vascular rather than primarily a proliferative and degenerative and secondarily a fibrotic lesion of the glomeruli the late or end stage is not very different in general type although certain changes so prevail as to give histological appearances that tell of the beginning and mode of progression of the lesion

In all of these kidneys vascular lesions are very prominent and usually involve blood vessels of all sizes in the kidneys Those lesions having in all probability the greatest influence on kidney function are those in the very small arteries and arterioles especially the afferent and efferent arterioles of the glomeruli In the arterioles the lesion is chiefly of the intima and mainly a thickening and subsequent or coincident hyalinization of the intima with decrease in size of the lumen Fatty infiltration of the hyalinized wall of such arterioles is very frequent These changes often are patchy in distribution along the course of the arteriole Thrombi often form at the site of these changes and hinder blood flow still more In larger arteries similar changes in the intima are frequent but often also there is hyaline transformation of the media without or with hypertrophy of the media In the larger arteries also there may be a thickening and cellular infiltration of the adventitia In some kidneys both in the intima and the media but especially in the intima, degeneration is more marked often in degree up to an actual necrosis giving rise to the term arteriolonecrosis of the kidney

Arteries large enough to have considerable elastic tissue show splitting and fragmentation of this When there is a distinct internal elastic lamina, this may break up or remain little changed while a new intima is formed making a distinct second internal elastic lamina inside the original one All of these lesions decrease blood flow in the kidney the decrease in vascularity is very evident in kidneys in which arterial injections have been made such injections show radical change in the vascular architecture of these kidneys With these vascular lesions there go on also degeneration fibrosis thrombosis and some cell proliferation and cellular infiltration of glomeruli and the same changes in the tubules as already described in an earlier paragraph giving a description of the changes encountered in chronic glomerulonephritis

Along with the changes just described interstitial tissue increases as in glomerulonephritis with the same general appearance except that in these kidneys it is relatively more vascular giving the red rather than gray color constituting a type of kidney which often is called the small red kidney of vascular nephritis

In the chronic pyelonephritis type of renal lesion the lesion is the result of bacterial inflammation with cellular infiltration of the interstitial tissue and proliferative and degenerative changes in glomeruli and tubules In the earlier stages numerous polynuclear leucocytes are mingled with the lymphocytes and

plasma cells that infiltrate the young connective tissue, i e connective tissue with numerous connective tissue cells or fibroblasts and newly formed blood vessels. Later polynuclear cells decrease and disappear, lymphocytes, plasma cells and fibroblasts become less numerous and the connective tissue grows denser Now in these kidneys glomeruli tubules and blood vessels often show such changes as already have been described in each of the preceding groups of cases, and sometimes these are so prominent as to make it look almost as if simultaneously three pathological processes bacterial pyelonephritis, glomerulonephritis and arteriolonephrosclerosis had been going on

With amyloidosis any of the already described histological appearances may be seen with the addition of amyloid deposits anywhere but chiefly in the glomeruli and arteries In the hypoplastic kidney which gives the clinical picture of chronic non edematous Bright's disease along with atrophy there is a defective blood supply increased interstitial connective tissue and degeneration and atrophy of glomeruli with secondary changes in the tubules consequent to atrophy of glomeruli

In the congenital cystic kidney, although the size may be very great, the clinical picture arises from the degeneration of glomeruli and tubules and the fibrosis of the interstitial tissue which without the cysts would constitute a small kidney, one with much the same structure as extensive, advanced chronic pyelonephritis It is only with the progressive enlargement of the many cysts that renal function is disturbed sufficiently to give the clinical picture of the form of chronic Bright's disease under discussion in this section

All of these forms of chronic renal pathology just described have in common three changes of progressively decreasing renal function They are (1) glomerular lesions of a nature to allow moderate leakage of albumin and increasingly to reduce the excretion of waste products, especially the non protein nitrogen substances (2) tubular lesions of a nature to restrict their normal function, a function chiefly of reabsorption and (3) vascular lesions to reduce total renal function by decreasing renal blood flow and also to cause focal changes in glomeruli and tubules in proportion to blocking influences on the nutritional blood supply to them changes which besides decreasing renal function contribute in various ways to raising general blood pressure a factor very important in causing various phases of the clinical picture of chronic non edematous Bright's disease

Heart

In almost every patient dying with chronic non-edematous Bright's disease the heart is hypertrophied and dilated sometimes very much so However, as a rule, except for increase in size the heart has a normal appearance, unless there has been a fibrinous pericarditis so called pericarditis uremica It is an interest

ing fact that these changes were well known to and commented upon by Richard Bright

A varying degree of arteriosclerosis of the coronary arteries is found Valves usually are normal or only slightly thickened Under the microscope the most frequent and often the only abnormality seen is enlargement of the muscle fibers and slight changes in the staining of their nuclei However there may be found various degenerative changes in the muscle fibers and small patches of peri vascular fibrosis If the coronary vascular system is well injected there will be found in the hypertrophied hearts a decrease in the number of capillaries about the muscle fibers proportionate to the increase in size of the fibers since with hypertrophy of muscle fibers there is no accompanying increase in the number of capillaries in the myocardium

Blood Vessels

Smaller blood vessels of the body show the same sort of lesions as have been described in the kidney Larger arteries often are dilated tortuous and thickened they show the changes of arteriosclerosis The distribution and degree of these vascular lesions vary much from patient to patient usually they are more marked in the kidney than in other organs In the brain and retina often vascular changes are extensive These as well as various other features of the pathology of chronic non edematous Bright s disease have been described in considerable detail in Part I under the general headings Pathogenesis Pathology and Pathological Physiology

Incidence

Chronic non-edematous Bright s disease is a frequently occurring condition often dominating the patient s condition while in other patients being of less marked severity It plays a secondary or complicating role in illnesses primarily of other origins The largest number of these patients are seen in the ages beyond 40 although chronic non-edematous Bright s disease can develop at any age down to young children

In the very old it is rare not to find in the kidney some of the lesions described in the preceding section although many of them have had during life only very minor disturbances of renal function often only slight albuminuria and a moderate number of hyaline casts in the urine As to sex if all of the various progressions of the renal lesion as described in earlier sections of the heading Chronic Non edematous Bright s Disease are taken into consideration there is no great pre ponderance in either sex although often it is stated that this form of Bright s disease is more frequent in men than in women

Symptomatology and Physical Findings

When one considers that patients with chronic non edematous Bright's disease show several different pathological processes in their kidneys, and that the pathogenesis of these lesions has taken on several different forms of progression from the primary lesion, it is surprising that, when the stage of chronicity has been reached, the general clinical picture is so much the same that, seen first at this stage often it is not possible to make a correct diagnosis of the pathology of the kidney To do this there is needed knowledge of the early stages of the Bright's disease In a certain number of patients history and early observation make clear the type of renal disease that has initiated what later becomes clinically chronic non edematous Bright's disease In numerous patients this knowledge is lacking often because these early stages have been so free from symptoms that the patients have had no medical observation

In contrast to chronic Bright's disease with edema this group has no dominating symptom The most frequently observed abnormal physical finding is high blood pressure The variety of symptoms encountered is large, and it is difficult, with regard to many of them to determine whether or not they are the result of the renal lesion, are characteristics of a certain type of individual prone to this type of Bright's disease or the result of some coincident or complicating disturbance Often there are no symptoms at all, the evidence of renal lesion being gained by examination of the patient, instigated by the discovery of anemia high blood pressure or albuminuria in some routine physical examination such as that incident to application for some form of life insurance or to the discovery by the ophthalmologist of changes in the retina suggesting Bright's disease as a cause What is very important to remember is that symptoms may be very slight and not suggestive of Bright's disease in some patients even when renal function already is markedly defective On this account not infrequently chronic Bright's disease is not recognized until some serious result occurs such as an attack of severe sometimes fatal uremia

Illustrative Cases

A condensed statement of the clinical and pathological study of a few typical patients with chronic non-edematous Bright's disease will serve as an illuminating introduction to a description of the various general and special features of this condition

Case XV is a patient in whom chronic non edematous Bright's disease began with an acute attack of Bright's disease of the hemorrhagic variety *Case XVI* is very similar to Case XV *Case XVII* is a patient in whom chronic non-edematous Bright's disease had an insidious onset without any recognized acute attack

to mark the beginning of the kidney disease *Cases XVIII* and *XIX* show a special type of Bright s disease with persisting red blood cells in the urine from onset to death the clinical picture shifting from acute hemorrhagic Bright s disease to subacute and chronic hemorrhagic Bright s disease *Case XX* is a patient in which disease began as the edematous or nephrotic type of Bright s disease then the edema disappeared and the clinical picture became that of chronic non edematous Bright s disease In all of these patients *Cases XV* to *XX* at death the kidneys showed the pathological lesions of chronic glomerular nephritis

Case XXI is a patient who for 12 years was known to have high blood pressure but remained a vigorous healthy woman then in 3 years signs and symptoms of chronic non-edematous Bright s disease appeared and progressed to a fatality *Case XXII* is a patient who after an acute attack apparently an exacerbation in the progression of a chronic non-edematous Bright s disease of unknown duration had evidences for 9 years of continuing chronic non-edematous Bright s disease which ended fatally complicated by cerebral hemorrhage In this patient the renal disease was superimposed on congenital aplasia of the kidney *Case XXIII* was a man who had hypertension for from 13 to 18 years There were repeated cerebral vascular accidents For 4 years before his death he had evidences of chronic non-edematous Bright s disease *Case XXIV* was an elderly woman, known to have hypertension for 12 years who during this period had a urine consistent with chronic non-edematous Bright s disease progressing slowly to a fatality In *Cases XXI XXII XXIII* and *XXIV* at death the kidneys showed the lesions of chronic vascular nephritis

Case XXV was a girl who following acute pyelonephritis beginning at the age of 3 continued to have in the urine evidences of kidney inflammation i e pyuria but for 9 years was well and developed normally Then evidences of renal insufficiency such as occurs in chronic non-edematous Bright s disease developed and progressed rapidly to her death in about a month with small kidneys fibrosed and showing greatly damaged glomeruli and tubules diagnosed pathologically as chronic pyelonephritis *Case XXVI* was a woman who following inflammatory renal lesions had evidences of renal insufficiency for 4 to 5 years slowly progressing until near the end when progression became rapid Her kidneys were much like those from Case XXIV

Case XXVIII which appears on a later page shows the clinical picture of chronic non-edematous Bright s disease in a patient whose kidney showed extensive amyloid infiltration *Case XXIX* on a still later page is one in which the pressure effects of many cysts in a polycystic kidney has hindered renal function in a way to produce a clinical syndrome similar to that of chronic non edematous Bright s disease caused by other types of renal lesions

Case XV — A young man of 18 was admitted to the hospital on Jan 10 1931 P B B H Med No 38273 again on Nov 12 1933 Med No 43894 and on Feb 21 1934 Med No 44460 He died on April 26 1934

SYMPTOMATOLOGY AND PHYSICAL FINDINGS

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Case XV —A young man of 18 was admitted to the hospital on *Jan 10 1931* P B B H Med No 38273 again on Nov 12 1933 Med No 43894 and on Feb 21 1934 Med No 44460 He died on April 26 1934

Four weeks before coming to the hospital on Jan 10, 1931 he had a rather severe cold with chill coryza and cough Three weeks before this admission moderate swelling of ankles and face was noted he began to have nausea and vomit his physician found blood in his urine Before this the patient had been in good health he had had no infectious disease The edema at first noted decreased and disappeared when the patient was kept in bed at home but reappeared in his ankles just before coming to the hospital

Physical Examination Jan 10 1931 — The skin appeared pale and pasty There was moderate ankle edema and abdominal distension The heart was slightly enlarged with a blowing systolic murmur loudest at apex and x ray showed slight enlargement Blood pressure was 162 mm Hg systolic and 105 diastolic Ophthalmoscopic examination showed only slight haziness of one side of left optic disc Urine had specific gravity ranging from 1 032 to 1 010 with a considerable amount of albumin many red blood cells moderate number of white cells and numerous casts hyaline, finely and coarsely granular and at first blood casts In the hospital red cells decreased but did not disappear At first his blood urea nitrogen was 32 mgm per 100 c c and phthalein excretion 22 per cent These changed gradually to blood urea nitrogen 14 mgm and phthalein 35 per cent Plasma protein early was 4 5 gm with albumin 2 4 and globulin 2 1 gradually increasing to 5 8 with albumin 3 3 and globulin 2 5 Red blood cell count ranged from a low of 2 730 000 to a high of 4 320 000 usually it was about 3 ,00 000 Leucocytes early were 14 200 and 15 400 falling slowly to 8 500 Hemoglobin ranged from 40 to 50 per cent Tonsils were removed during this period and showed chronic tonsillitis with fibrosis After discharge x ray showed his heart to return steadily to normal size Urine continued to show albumin as while in the hospital but the sediment very largely cleared blood urea nitrogen fell to 8 mgm per 100 c c., phthalein increased to 55 per cent plasma protein to 6 7 gm with albumin 4 4 and globulin 2 3

In about May 1933 morning headaches began with nausea and occasional vomiting in Sept 1933 eye grounds for the first time showed definite changes with cotton wool spots and tortuous vessels blood pressure now was increasing and in Oct 1933 was 230/154 On Nov 10 there was a severe nosebleed On Nov 12 he came again to the hospital I B B H Med No 43894

Physical Examination Nov 12 1933 — There was no pallor no edema Heart was very slightly enlarged on both physical and x ray examination and without murmurs Blood pressure was 220/190 Ophthalmoscopic examination showed swelling of both optic discs markedly tortuous vessels and scattered irregular whitish areas with suggestive left macula star but no hemorrhages Urine had specific gravity ranging from 1 020 to 1 013 with a slight amount of albumin and few red and white cells and occasional casts hyaline granular or cellular Hemoglobin was 88 per cent, red cell count 4 850 000 white cell count 14 400 falling to 8 300 Blood urea nitrogen was 30 mgm, fasting in 100 c c and phthalein excretion 45 per cent Plasma protein was 5 8 gm with albumin 3 5 and globulin 2 3 He remained in the hospital to Dec. 6 1933 with blood pressure stabilizing at 180 to 190 mm Hg systolic and 130 to 160 diastolic

At home the patient remained in bed as he had done throughout much of his illness and his condition was about as when he left the hospital until Feb 21 1934 when he developed severe lower abdominal cramps vomited about a dozen times, had a terrific

headache and about 7 P M had a generalized convulsion He was again admitted to the hospital on Feb 21 1934 P B B H Med No 44460

Physical Examination, Feb 21 1934 — Patient was unconscious looked sallow and pasty showed no edema Heart was about as on previous admission blood pressure was 240 mm Hg systolic and 170 diastolic Ophthalmoscopic examination showed what was found at his previous admission with in addition numerous hemorrhages of varying shape and size some quite large in the right fundus none in the left Urine had a specific gravity of 1 024 a very slight trace of albumin with no cells and no casts in the sediment Hemoglobin was 82 per cent red cell count 4 200 000 and white cell count 18 100 Blood urea nitrogen on admission was 12 8 mgm and next day 34 mgm per 100 c c Plasma protein was 7 1 gm with albumin 4 2 and globulin 2 9 Two weeks later phthalein excretion was 35 per cent Just before death blood urea nitrogen was 22 mgm per 100 c c

Soon after admission the patient had a second generalized clonic convulsion and on the next day a third Mentally he cleared and his general condition was much as during his previous admission Nov 12 to Dec 6 1933 On Apr 8 he was not so well with nausea headache and drowsiness On Apr 19 he developed left 7th nerve palsy but his general condition had become better On Apr 26 he had a staring expression labored breathing and could not be aroused his blood pressure was 290/200 One hour and forty minutes later he died

Autopsy — Diagnoses nephritis chronic glomerular cardiac hypertrophy cerebral hemorrhage right stomach ulcerations

Heart weighed 620 gm but valves and myocardium appeared essentially normal Coronaries showed numerous atheromatous plaques without calcification there was no coronary obstruction The *stomach* showed numerous small mucosal hemorrhages a few with ulceration Histologically there was extensive arteriolar degeneration in these areas with necrosis of glandular epithelium and fibrin and red cell and polynuclear filtration *Kidneys* weighed 140 and 130 gm each Surface was slightly granular after capsule easily was stripped off Color and appearance of cut surface of kidneys seemed normal Microscopically the glomeruli very generally showed capsular proliferation capsular adhesions and partial or complete fibrosis There was almost no cellular infiltration of kidney Arterioles showed slight to moderate hyalinization and thickening of their walls Many tubules were dilated There was very slight scarring anywhere in the kidney *Brain* showed marked edema a large right frontal lobe hemorrhage with hemorrhage in the right and left ventricles

Summary of Case XV — A man of 18 previously always well about Dec 10 1930 had a severe cold One week later moderate swelling of ankles and face were noted nausea and vomiting followed urine became bloody On Jan 10 1931 he looked pale *had moderate edema of his ankles his heart was slightly* enlarged left optic disc was hazy blood pressure was 16 / 105 Urine had specific gravity of 1 032 considerable albumin many red blood cells moderate number of white cells numerous casts bloody granular and hyaline Phthalein excretion was 22 per cent blood urea nitrogen 32 mgm per 100 c c plasma protein 4 5 gm with albumin 2 4 and globulin 2 1 Hemoglobin was 40 to 50 per cent red

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TABLE XIII

URINE EXAMINATIONS AND TESTS OF RENAL FUNCTION CASE XVI

Date	4 Hr Amt	Sp Gr	Alb	Casts Hy	Casts Gran	R B C	W B C	Ph	B U N	Bl Cl	Wt
1917	(From	Boston	City H	ospital	record	s.)					
July 7		1 0 0	++								
July 9		1 018	++								
July 1		1 012	++								
July 14		1 016	++								
July 15		1 016	++		+		+				
July 16		1 014	++		+						
July 31		1 016					++				
Aug 1		1 014	++	++	++	++	+++				
Aug 4		1 008	++		++						
Aug 8		1 006	++			+	++				
Aug 15								30 %			
1918	(From	Peter B	ent Bri	ha n	Hospit	al reco	rds)				
Mar 4			+	+	++	+					43 7
Mar 6	1 00	1 011	+	++	++	+	+				
Mar 9								0 %			
Mar 30			+	+	++		+				
Apr											44 6
Apr 16	,50	1 021	+++	+++	+	+	+	45 %	18 0	5 00	45 0
May 21			+++	+++	+		+				44 6
June 11	2 000	1 014	++	+++	+		+	3 %	0 1	5 36	44 6
July 30	1 000	1 012	++	+			+				44 6
Sept 4	1 50	1 014	+++	+++	+		+++	3 %	18 1	4 56	47 8
Sept 5	,50	1 014	++	+			+				45 4
Nov 19											45 4
1919											
Jan 7	500	1 019	++	+	+	+	+++	24 %	20 0		45 8
Feb 0	500	1 013	++	+			+				45 8
Feb 26								2	40 0	5 04	45 4
Apr 24	500	1 015	++	++	++		+++	6 %	13 0	4 66	46 0
June 26		1 011	++	+			+				44 8
June 8	500	1 014	++	+	+	+	+				
Sept 11	500	1 011	++	+		+	+++				46 2
Sept 15	500	1 011	++	+	+	++	++	5 %	33 0	4 75	44 6
Sept 16	950	1 010	+				+				44 6
Sept 17	2 390						+	5 %			44 2
Sept 18	1 950	1 008	+	++	++		+				43 4
Oct 2		1 011	++		+		+				46 4
Oct 30	1 50	1 014	++	+			+	5 %	52 0		46 4
Nov 21	1 50	1 014	++		+	+++	+	+	,6 0		46 8
Dec 3	1 500	1 006	++	+	+		+				46 2
19 0											
Jan 6	†S S	1 010	++				+				
Jan 7								+	1 1 0		44 2
Jan 12								0	206 0	6 96	43 0
Jan 13	350	1 018	+++				+++				
Jan 17	Died										

Sp Gr = Specific Gravity Alb = Albumin Hy = Hyaline Gran = Granular R B C = Red blood cell W B C = White blood cell Ph = Phenolsulphonephthalein excretion in two hours B U N = Blood urea nitrogen in milligrams per 100 c c of blood Bl Cl = Blood chlorides in grams per liter of blood Wt = Weight in kilos

† S S = Single specimen
+ = Very slight trace of albumin
++ = Slight trace of albumin
+++ = Much albumin
++++ = Very much albumin

+ = Rare
++ = Numerous
+++ = Many
++++ = Very many
+ = Trace

blood cells 2,700,000 to 4,320,000 and leucocytes 14,200 to 15,400 Over a period of 17 months urine showed less and less in the sediment but always a few red blood cells and casts and always considerable albumin, red cell count rose to 4,850 000 white cells were about 8 500 and hemoglobin 40 to 50 per cent, plasma protein gradually increased Then in May 1933 morning headaches, nausea and vomiting began, and in Sept 1933 eye grounds showed tortuosity of blood vessels and cotton wool spots Blood pressure rose, and in Oct 1933 was 230/154 On Nov 10, 1933 there was a severe nosebleed After a stay in the hospital blood pressure ranged from 180/130 to 190/160 In Feb 1934 lower abdominal pain vomiting and terrific headache developed followed by generalized convulsions and stupor with blood pressure 290/200 Eye grounds now in addition to previous findings showed hemorrhages Urine now showed very little albumin, no casts and no cells There was no azotemia 'Phthalein excretion was 34 per cent, and plasma protein was 7 1 gm Convulsions ceased, and patient was brighter with little headache, but on Apr 8 he was again drowsy with headache on Apr 19 he developed left 7th nerve palsy and on Apr 26 he could not be aroused had labored breathing and died Duration of his disease from onset as acute hemorrhagic Bright s disease was 4 years and 5 mos Autopsy showed chronic glomerular nephritis with kidneys shrunken to about half normal size and heart hypertrophy with heart size about twice normal size

Case XVI — A young woman of 29 was admitted to the hospital on September 15, 1919 Med No 11839 and discharged on September 19 1919 again admitted January 6 1920 remaining until her death January 17 1920 The patient s habits have been good She takes one cup of coffee daily no tea tobacco drugs and alcohol except for a moderate use of beer

Previous History — She had measles, mumps and whooping cough in childhood and tonsillitis frequently She has had numerous attacks of malaria every year She had acute rheumatism 7 years ago and again 2 years ago There is no history of chicken pox smallpox diphtheria influenza chorea pleurisy pneumonia scarlet or typhoid fever Nothing in the patient s history indicated any period of acute Bright's disease

Present Illness — When she was in the City Hospital 2 years ago (1917) with her second attack of acute rheumatism she was found to have acute Bright s disease (see Table XIII for record of urine) Since then she has been carefully followed by Dr O Hare and her record shows that her condition steadily has grown worse On April 16 1918 her blood urea nitrogen was 18 mgm per 100 c c her 'phthalein 45 per cent and blood pressure systolic 128 mm Hg diastolic 80 mm Since then her kidney function has decreased steadily until at the time of entrance to the hospital on September 15 1919 her blood urea nitrogen was 33 mgm per 100 c c phthalein 5 per cent and blood pressure systolic 188 mm Hg diastolic 112 mm

Physical Examination on Sept 15 1919 — This showed a well developed and nourished middle aged mulatto mentally clear and cooperative *Heart* — Apex impulse was seen and felt in the fifth interspace 8 cm from the midline The left border of

TABLE XIII

URINE EXAMINATIONS AND TESTS OF RENAL FUNCTION CASE XVI

Date	24 Hr Amt	Sp Gr	Alb	Casts Hy	Casts Gran	R B C	W B C	Ph	B U N	Bl Cl	Wt
1917	(From Boston City Hospital records)										
July 7		1 0 0	++								
July 9		1 018	++								
July 1		1 012	++								
July 14		1 016	++								
July 15		1 016	++		+		+				
July 16		1 014	++		+						
July 31		1 016					++				
Aug 1		1 014	++	++	++	++	+++				
Aug 4		1 008	++		++						
Aug 8		1 006	++			+	++				
Aug 15								30%			
1918	(From Peter Bent Brigham Hospital records)										
Mar 4			+	+	++	+					43 7
Mar 6	1 200	1 011	+	++	++	+	+				
Mar 9								20%			
Mar 30			+	+	++		+				
Apr 2											44 6
Apr 16	750	1 021	+++	+++	+	+	+	45%	18 0	5 00	45 0
May 21			+++	+++	+		+				44 6
June 11	2 000	1 014	++	+++	+		+	32%	0 1	5 36	44 6
July 30	1 000	1 012	++	+			+				44 6
Sept 24	1 250	1 014	+++	+++	+		+++	3 %	18 1	4 56	47 8
Sept 25	,50	1 014	++	+			+				45 4
Nov 19											45 4
1919											
Jan 7	500	1 019	++	+	+	+	+++	24%	0 0		45 8
Feb 0	500	1 013	++	+			+				45 8
Feb 6								2%	46 0	5 04	45 4
Apr 24	500	1 015	++	++	++		+++	26 %	13 0	4 66	46 0
June 6		1 011	++	+			+				44 8
June 8	500	1 014	++	+	+	+	+				
Sept 11	500	1 011	++	+		+	+++				46 2
Sept 15	500	1 011	++	+	+	++	++	5%	33 0	4 75	44 6
Sept 16	950	1 010	+				+				44 6
Sept 17	2 390						+	5%			44 2
Sept 18	1 950	1 008	+	++	++		+				43 4
Oct 22		1 011	++		+		+				46 4
Oct 30	1 750	1 014	++	+			+	5%	52 0		46 4
Nov 21	1 750	1 014	++		+	+++	+	+	6 0		46 8
Dec 3	1 500	1 006	++	+	+		+				46 2
19 0											
Jan 6	†S S	1 010	++				+				
Jan 7								+	121 0		44 2
Jan 12								0	206 0	6 96	43 0
Jan 13	350	1 018	+++				+++				
Jan 17	Died										

Sp Gr = Specific Gravity Alb = Albumin Hy = Hyaline Gran = Granular R B C = Red blood cell W B C = White blood cells Ph = Phenolsulphonephthalein excretion in two hours B U N = Blood urea nitrogen in milligrams per 100 c c of blood Bl C = Blood chloride in grams per liter of blood Wt = Weight in kilos

† S S = Single specimen
+ = Very slight trace of albumin
++ = Slight trace of albumin
+++ = Much albumin
++++ = Very much albumin

+ = Rare
++ = Numerous
+++ = Many
++++ = Very many
+ = Trace

Two Hour Renal Test September 17 1919 Case XVI

Time	*Volume*	*Sp Gr*	*Urea Per Cent*	*Chloride Gms*
7 9 a m	135	1 017	27	36
9 11 a m	188	1 014	31	58
11 a m 1 p m	140	1 012	30	42
1 3 p m	148	1 013	18	27
3 5 p m	163	1 013	33	54
5 7 p m	210	1 010	27	57
7 9 p m	196	1 011	29	57
9 p m 7 a m	770	1 013	15	1 16
Total	1 950			4 47
Night	966			

In the two-hour test there is a total and a night polyuria and definite fixation in specific gravity except in one portion

Blood Pressure Case XVI

	Systolic	*Diastolic*
March 4 1918	120	80
April 2 1918	110	80
April 16 1918	1 8	80
May 4 1918	124	80
June 11 1918	120	80
July 30 1918	116	80
September 24 1918	124	96
November 11 1918	136	100
January 7 1919	120	96
February 20 1919	148	100
February 26 1919	158	
April 24 1919	16	100
June 26 1919	168	102
June 28 1919	166	100
September 11 1919	172	
September 15 1919	188	112
October 22 1919	190	116
October 30 1919	166	100
November 17 1919	204	1-8
November 21 1919	172	102
December 3 1919	174	102
January 6 1920	188	1 5
January 14 1920	180	12

Wassermann Reaction September 16 1919 blood serum, negative

Blood Counts Case XVI

	W B C	*R B C*	*Hb*
June 28 1919		2 776 000	50%
September 15 1919	8 200		85%
September 18 1919		3 552 000	65%
October 30 1919		3 968 000	55%
January 6, 1920		2 030 000	50%

dullness was 10 cm to the left of the midline the right border of dullness was not beyond the sternal margin The sounds were regular and of good quality there was a well marked presystolic gallop rhythm best heard at the apex where there was heard also a blowing systolic murmur No thrills were palpable *Vessels* — Radial pulses were equal regular and of good volume and tension The vessel walls were palpable and slightly sclerosed The brachials were sclerosed the temporal not palpable

Eyes April 4 1918 — O D disc normal Both disc veins pulsated Retina was normal no exudate no hemorrhages Retinal arteries were rather straight and still with practically no pressure effect at crossing of artery and vein One vein wound over and under the arteries One artery showed slight unevenness in reflex O S disc slightly irregular Both veins pulsated The retina showed no exudate no hemorrhage The arteries as in O D except that there was more unevenness not only of reflexes but also of the lumina of the vessels The supranasal artery looked almost beaded There was practically no nicking of veins which are of normal size

Eyes October 2 1919 — O D disc normal Arteries showed very slight pressure effects One or two showed narrowing over a small area There was a mottling of the blood column *Along the side of a small vessel running parallel to the supranasal artery* was a small white spot about 1½ cm in diameter No hemorrhages are seen O S discs normal Arteries showed slightly greater pressure effects and more marked though not greatly marked narrowing and constriction effect This was best seen in the supra nasal artery There was no exudate no hemorrhage no tortuosity of vessel in either eye

Second Entry January 6 1920 Present Illness — The patient was readmitted on January 6 1920 on account of the fact that in following her case her kidney function tests revealed a progressive diminution in kidney efficiency and in addition she seemed to be developing symptoms of an approaching uremia Five days before admission there was an acute exacerbation of her dyspnea which became quite marked She was forced to be propped up in bed and even then breathing was difficult Associated with the dyspnea was a cough productive of a sputum which frequently was tinged with bright red blood At this time she noticed an impairment of vision which rapidly was progressive to the point where she was unable to read the ordinary sized print On her admission in September 1919 she had felt there was no change in her vision There is vomiting irrespective of food taken which had been prominent during 5 days The vomitus had been streaked with bright red blood at times

Physical Examination January 6 1920 — The patient was a well developed under nourished female mulatto lying propped up in bed and experiencing labored breathing Altogether aside from her natural light brown color she looked pale and pasty Mentally she was clear *Nose* — There was a small bleeding point on the anterior portion of the septum on the left side *Mouth* — Breath was slightly urinous *Tongue* was coated *Heart* — Apex impulse was felt in the fifth interspace 10 cm from the midsternal line It was not visible There were no thrill The left border of dullness was 14 5 cm from the mid ternal line and the right border of dullness 3 5 cm The supracardiac dullness measured 5 cm in the second space There were no murmurs no friction rub The pulmonic second sound was greater than the aortic second and was ringing in character The heart sounds were clear regular but rather rapid *Vessels* — Radial pulses were

equal and regular rate was 124 per minute The vessel walls were palpable and lightly sclerosed *Blood pressure* was systolic 188 mm Hg diastolic 123 mm *Lungs* — Tactile fremitus was not remarkable Percussion revealed no definite dullness anywhere There were heard crepitant rales over the front below th clavicle on the right side audible during inspiration Similar rales were heard over the base behind on the right side extending to about the angle of the scapula also audible during inspiration The presence of such rales over the left lung was doubtful but on this side the breath sounds especially over the back apparently were approaching bronchial in character The breath sounds on the opposite side were not altered No pleural friction rub was heard *Extremities* — Very moderate edema of the lower legs was present

Blood CO — January 7, 1920 31 mm January 12 1920 2 mm

Eyes January 13 1920 — O D disc apparently normal To the inner side of the disc was a long spine like hemorrhage and above and to the other side of this a few linear hemorrhages There was a moderate amount of cotton wool exudate scattered around the disc and one large area in the region of the macula In spite of the fact that the patient complained of darkness of vision she could count fingers perfectly The arteries showed moderate unevenness and pressure effects wall brighter than normal O S disc slightly irregular in outline its surface was yellowish white apparently with no cupping No hemorrhages were seen Scattered moderately large areas of cotton wool exudate were seen around disc but not close to it

January 17 1920 — Twitching began on the second day in the hospital and continued with a slight increase in frequency and extent until death She developed a mild exophthalmos and some itching of her skin For the last 3 days she has been semicomatose and has had dyspnea and air hunger Her respirations on the day before she died went down to 15 Blood urea nitrogen which had been 121 mgm soon after admission went up to 250 mgm per 100 c c Phthalein excretion was zero This morning her respirations became weaker and stopped She died at 3 10 A M

Autopsy — Diagnoses nephritis chronic diffuse pericarditis fibrinous hypertrophy of heart edema of lungs hydrothorax bilateral gastritis acute cystitis acute fibroids of uterus pleuritis fibrous lower lobe of right lung bronchopneumonia organizing arteriosclerosis *Kidneys* — each kidney weighed ,0 gms The capsule stripped with some difficulty revealing a symmetrically granular surface The granular appearance was due to the presence of numerous white opaque nodules averaging ½ to 1½ mm in diameter which were scattered diffusely over the surface and between which there were red depressions giving the surface as a whole a reddish gray color The consistency was firm The parenchyma itself was thinner than normal averaging only 1¼ to 2 cm The cortex was narrowed its average measurement being about 2 to 3 mm The cut surface was reddish gray in color with a suggestion of fine granulation being not as smooth as the cut surface of normal kidney tissue Small vessels were sclerotic The color of the cortex was reddish gray which was brought about by the presence of grayish opaque areas which were studded with small reddish striations giving to the whole the reddish gray appearance The medullary rays did not stand out as prominently as normal and the individual rays seemed interspersed with areas of grayish opaque appearing tissue The medulla was a darker grayish red color and the rays here were separated by streaks of grayish tissue The pelvis was normal The

ureters were normal The microscopic sections of the kidney in general showed a very marked degree of general fibrosis of the cortex atrophy and dilation of the tubules sclerosis of the arteries and hyalinization of the glomeruli Irregular intimal fibrous thickening was present in the arcuate arteries and was progressively more prominent in the various branches of these vessels resulting in places in obliteration of some of the terminal arteries and arterioles No progressive acute lesions in the vessels were noted The glomeruli were involved universally and severely Many of them were completely obliterated by fibrous induration Others showed varying degrees of thickening of capillary walls within the tuft glomerular adhesions and capsular thickening In the better preserved glomeruli more minute changes were evident Some of the capillaries were plugged by minute hyaline masses There was a progressive degeneration of the epithelial cells lining the tuft and covering the capsular space This was indicated often by marked swelling of these cells and the accumulation within their cytoplasm of numerous hyaline droplets These cells sometimes were desquamated within the capsular spaces

The tubules showed varying degrees of atrophy and dilatation Only a small proportion of the tubules could be recognized as remnants of the convoluted portion The tubules frequently were dilated often enfolded The epithelium varied in size sometimes hypertrophic and at other times atrophic staining pink and appearing granular Other tubules were dilated and lined by flat atrophic epithelium Still others were contracted by a greatly thickened hyaline basement membrane The contents of these tubules were various The larger dilated tubules might contain plugs of fibrin coagulated granular precipitate red blood corpuscles polymorphonuclear leucocytes or clear vesicular bodies Others contained hyaline casts The tubular epithelium about some of these tubules containing casts had undergone necrosis and numbers of polymorphonuclear leucocytes had been attracted to the spot and fibroblasts were growing into the focus

There was a marked degree of fibrosis throughout the kidney cortex more dense toward the periphery looser and more vascular nearer the medulla In these very vascular areas small extravasations of blood were not uncommon and here and there were accumulations of mononuclear cells of the lymphocyte type

Summary of Case XVI — A woman of 29 at the age of 27 while suffering from rheumatism was found to have acute Bright s disease Frequent attacks of tonsillitis may have been the cause of her Bright s disease Her renal condition steadily grew worse On April 16 1918 her blood urea nitrogen was 18 mgm phthalein excretion 45 per cent and systolic blood pressure 128 mm Hg and diastolic 80 From this level progression was steady with a level of blood urea nitrogen of 33 mgm phthalein 5 per cent and systolic blood pressure of 188 mm Hg and diastolic 123 on September 15 1919 She rapidly grew worse blood urea nitrogen rose to 206 mgm and acidosis developed she died on January 17 1920 At the end of her clinical course she had some edema nausea and vomiting retinopathy and much respiratory distress She developed muscular twitching became comatose and at the end had air hunger At autopsy the kidneys were

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small finely granular, with glomeruli showing advanced chronic lesions much increase of connective tissue and atrophy of renal tissue This patient is of the type of steadily progressing chronic non edematous Bright's disease with a rather short duration of disease (about 3 years) causing increasing blood pressure and decreasing kidney function the lesion having progressed finally into the late stages of chronic glomerulonephritis

Case XVII — A young woman of 23 was admitted to the P B B H Med No 2833 on May 22 1915 and discharged July 5 1915 She was readmitted on November 2 1916 and discharged November 11 1916 She was in the hospital a third time from April 8 1918 to July 2 1918 and a fourth time from November 30 1918 to December 12, 1918 on which date she died

On May 22 1915 she gave the following history

Past History — *Infections* — A lymph node in the right side of the neck was opened at 7 years She had whooping cough at 8 scarlet fever at 9 and measles at 10 years All these were slight attacks and without sequelae She had anemia for two winters was 3 months in bed 5 years ago and 1 month 4 years ago In the history there was nothing to suggest a period of acute Bright s disease

Present Illness — About 4 years ago without assignable cause she was bothered after she arose in the morning by headaches in her forehead or the top of the head only twice in the back of the head They have been occasionally on one side or the other of the head but generally on both sides Their frequency was once a fortnight until about 10 months ago then every week generally on Saturday mornings Beginning 3 months ago they came 3 or 4 times a week and then for a month nearly every day Later in the morning they became worse and remained the same until about 6 P M or even till mid night For the last 2 weeks they came on later in the morning toward noon They were not affected for better or worse by reading exercise leaning forward eating catamenia or anything else The onset was gradual so that before about half of the attacks she could predict them the preceding evening by a heavy feeling in her head Their severity generally had been moderate Perhaps 1 in 6 was so severe that it kept her in bed prostrated by the attendant vomiting which lasted all day and continued even with bland fluids She was not troubled by nausea except for about a minute just before the vomiting Her bowels were apt to be loose at these times She had one dizzy spell this winter on getting up quickly out of bed but she did not fall She has had no other such spells before or since She has had no eye symptoms during attacks but she has had blurring of one or the other eye at unexpected times for 5 or 6 years

Physical Examination on May 22 1915 — A fairly well developed and slender girl who looked more like 19 than her given age of 23 years and appeared healthy although not robust and was perfectly comfortable and answered alertly *Eyes* — The pupils were large circular equal and did not contract readily for near vision although she had had no medicine locally or generally but do contract to light *Ophthalmoscopic examination* showed media clear fundi of good color throughout and the discs normally well outlined No areas of exudation or hemorrhage were made out The veins and arteries were normal in every respect *Heart* — The apex was just felt in the fifth space and percussed there 10½ cm from the midsternum The upper border was at the

third rib The right border and supracardiac dullness did not extend beyond the sternal edge No thrills were felt At the apex the first sound was of good quality and the second sound was heard Rhythm was regular rate 90 At the base the pulmonic second sound was greater than the aortic second No murmurs were heard *Vessels* — The pulses were equal synchronous, of good volume and tension The wall were not sclerosed *Blood Pressure* (Table XVI) was systolic 165 mm Hg diastolic 120 mm Her urine (Table XIV) had a specific gravity of 1 006 with a slight trace of albumin and a few hyaline and granular casts Her phthalein excretion was 12 per cent and her blood urea nitrogen 58 7 mgm per 100 c c (see Table XIV)

During this stay in the hospital there was no essential change in her condition The patient felt very well on leaving the hospital in July 1915 went on a vacation and did not work but in a few months she began to be troubled with headaches again At first they were present when she awoke in the morning and she had them once a week Later they often came on during the day The frequency increased and in April 1916 she was having 3 to 4 a week These headaches usually became better about 7 P M but occasionally she fell asleep without relief She did not vomit now with them Of late she had been unable to eat the restricted diet laid out for her when she left the hospital in July 1915

On readmission November 2 1916 she had a worried expression Her skin was pale and of a lemon yellow color She had the same degree of anemia as before (see Table XV) Her lips were a little cyanotic The heart seemed a little larger the percussion outlines being 11 cm to the left and 3 cm to the right of the midsternal line Otherwise physical examination was as before The eye grounds were unchanged Renal function and urinary findings were the same as before (see Table XIV) No essential change took place in her while in the hospital this time On returning home her condition was much as it had been before she was able to work most of the time until April 1918

On April 5 1918 she awoke quite early in the morning with a severe frontal headache She took some aspirin but this did not relieve her She went to work but had to return home at 1 30 P M because the headache was getting worse and she had much blurring of her vision She had no pains but felt sick all over The headache persisted until 4 P M on April 8 The previous morning she noticed a swelling of her neck especially below the left jaw A few minutes later her right mandibular region was affected similarly The swelling extended the full length of her jaw and up onto the cheeks for several centimeters On April 8 her mastoid regions and upper two-third of the sternum were swollen also These area were not red but were slightly tender to touch although they did not ache or cause pain except when touched She vomited once at 9 A M April 8 She entered the hospital again on Monday morning April 8 1918

Physical Examination now (April 1918) showed a patient fairly well developed and nourished conscious and rational *Face* showed a large swelling in the left mandibular region more marked below the jaw but extending several centimeters onto the cheeks and from symphysis to angle of jaw There was a similar swelling on the right side but it was not very marked Both mastoid regions were swollen These swollen areas were not red did not ache and were painful only when touched This condition was one of a slightly pitting edema *Ophthalmoscopic examination* showed vessel more tortuous than normal both discs were very indistinct one or two small recent hemorrhages

TABLE XIV

URINE EXAMINATIONS AND TESTS OF RENAL FUNCTION CASE XVII

Date	24 Hr Amt	Sp Gr	Alb	Casts Hy	Casts Gran	R B C	W B C	Ph	B U N	Bl Cl	Ht
1915											
May [illegible]	1 300	1 006	*++								4 2
May 24	1 000	1 006	++	**+	**+			1[illegible]%			
May 26	1 390								58 7[illegible]		
May 30	1 [illegible]90		1 [illegible] gm per lit	+++	+++			16%			
June 6	4[illegible]5	1 011	2 gm	+	+	**++	** +++				
June 9	1 400							18%			
June 10	1 400										44 6
June 14	1 325								62 50		
June 16	1 [illegible]	1 009	2 gm	+	+						
June 17	1 37[illegible]										44 4
June 21	975							13%			
June 23	1 575	1 008	1 3 gm	+			+				44
July 1	1 300	1 013	1 4 gm				+				44 [illegible]
1916											
Nov 2	906	1 006	+++	+	+		+		53 5[illegible]	5 5	4[illegible] 2
Nov 3	[illegible] 150							13%			
Nov 4	1 575	1 003	+++	+			+				
Nov 10	1 [illegible] 5										44 2
Nov 11		1 006	+++	+			+				
1918											
Apr 9	9[illegible]5	1 010	+++			+	+++	* *			
Apr 10	10 5	1 009	+++		+	+	+	+			
Apr 12	1 575								97 7	5 04	40 6
Apr 15	850	1 010	+++			+	++				40 4
Apr 19									154 1	4 19	
									150 1	4 23	
Apr [illegible]0	2 [illegible]								144 8	4 0	
Apr 23	1 500								168 3		
Apr [illegible]6									152 4	4 20	
Apr [illegible]8											41 6
Apr 30									140 3	4 66	
May 1								+			
May 3									1 9 4	4 84	40 2
May 7	550	1 005	++				+				
May 9								+	109 [illegible]	5 44	
May 14		1 006	++		+		+				
May 1[illegible]								+	101 1	5 [illegible]0	
May 19											3[illegible] [illegible]
May 24		1 010	++								
May 31								2%	90 1	[illegible] 93	
June [illegible]		1 006	++								
June 4								+	86 4	5 78	
June 11		1 010	+++				+	+	[illegible]5 8	5 93	
June 1[illegible]	850										38 6
June 18	900	1 007	++	+			+++				
June [illegible]6	750								64 8	5 78	
June 27	1 090							+			38 0
June 28	1 750	1 006	++	+	+		+++				38 0
July 2											

TABLE XIV (Cont)

URINE EXAMINATIONS AND TESTS OF RENAL FUNCTION CASE XVII (CONT)

Date	24 Hr Amt	Sp Gr	Alb	Casts Hy	Casts Gran	R B C	W B C	Ph	B U N	Bl Cl	Wt
1918											
Dec 1	1 088	1 011	++			+	+++				
Dec 4									89 0	5 03	
Dec 8	1 055	1 012	++		+	+	+++		++		
Dec 10	451	1 013	++		+	+	+				
Dec 11								+	1 0 0	4 4[illegible]	
	Blood 1/2 hour post mortem								145 0		

Sp Gr = Specific Gravity Alb = Albumin Hy = Hyaline Gran = Granular R B C = Red blood cells. W B C = White blood cells Ph = Phenolsulphonephthalein excretion in two hours B U N = Blood urea nitrogen in milligrams per 100 c c. of blood Bl Cl = Blood chloride in grams per liter of blood Wt = Weight in kilos.

+ = Very slight trace of albumin	+ = Rare
++ = Slight trace of albumin	++ = Numerous
+++ = Much albumin	+++ = Many
++++ = Very much albumin	++++ = Very many
+ = Trace	

TABLE XV

BLOOD COUNTS CASE XVII

	W B C	R B C	Hb	
May 22 1915	7 500	3 150 000	56%	
November 2 1916	8 800	3 07[illegible] 000	58%	
November 10 1916	8 800	4 864 000	6[illegible]	
April 9 1918	10 [illegible]00		80	
April 10 1918		3 056 000		
May 16 1918	5 000	2 6[illegible]4 000	60 (T)	
May 27 1918	5 [illegible]00	3 [illegible]80 000	[illegible]5 (T)	74% (P)
June 21 1918	[illegible] 600	4 224 000	70% (T)	66% (P)
June 28 1918	6 [illegible]00	3 832 000	75% (T)	100% (P)
November 30 1918	6 000	2 [illegible]20 000	50 (T)	
December 5 1918		2 856 000		

T = Talquist Method
P = Palmer Method

TABLE XVI

BLOOD PRESSURE CASE XVII

	Systolic	Diastolic
May 22 1915	165	110
May 29 1915	139	100
June 10 1915	135	105
June 28 1915	124	92
July 7 1915	122	95
November 2 1916	160	120
April 9 1918	190	1 0
April 22 1918	170	120
April 30 1918	110	72
May 8 1918	118	75
May 16 1918	122	84
May 24 1918	140	100
June 5 1918	150	100
June 18 1918	155	100
July 1 1918	140	100
November 30 1918	210	130
December 2 1918	200	130
December 9 1918	202	120

were seen in each eye no exudate was present *Heart* was as on the last admission except now a systolic murmur was heard all over the precordium best at the apex *Vessels* — Radial pulses were equal and rapid rate 110 the vessel walls were not remarkable Blood pressure (Table XVI) was 190 mm Hg systolic and 120 mm diastolic There was no edema of the legs and no edema of the sacral region or back For urine renal function and blood see Table XIV

April 18 1918 The breath now was markedly urinous The patient seemed definitely worse than at entrance at which time her renal function was extremely poor

April 23 1918 Four days ago the patient's blood CO_2 was found to be 16 mm With this she became quite drowsy refused nourishment and vomited several times Also a few muscle twitchings were noticed her blood urea nitrogen had gone up to 155 mgm per 100 c c of blood Preparation was made at once for the removal of blood from her vein but before this could be done the patient had a typical uremic convulsion However blood was removed and the red cells washed several times in salt solution and reintroduced A few hours later the patient was given 200 c c of a 5 per cent solution of sodium bicarbonate intravenously Following this she had a second convulsion swallowed her tongue and almost stopped breathing She remained comatose for 2 days when she became better and was able to recognize her mother and talk However she was somewhat confused until yesterday when she became quite clear, and a marked improvement was noted in her general condition The patient has had no convulsions for the past 3 days

May 1918 Patient has been very comfortable for the last week There have been no convulsions and the patient has slept fairly well at night The blood urea nitrogen has fallen somewhat being now 140 mgm in 100 c c Breath is not urinous

May 11 1918 The phthalein excretion is still only a trace, but the blood urea nitrogen now has dropped to 109 5 mgm The urinary picture shows no particular

change There had been no twitching recently and the patient on the whole was very comfortable

May 16 1918 The alveolar CO_2 on May 13 was 32 5 mm The urine contained a slight trace of albumin a few granular casts and white blood cells but no red blood cells The phthalein remained only a trace The blood urea nitrogen had dropped to 101 1 mgm per 100 c c The hemoglobin dropped from 80 per cent on admission to 60 per cent today There had been no twitching during the last few days and in general the patient had been very comfortable and was looking very much better than a month ago

May 19 1918 Yesterday the patient received a blood transfusion of 850 c c Following this the temperature rose to 102 F and the pulse to 120 but there was no real chill and the patient was feeling all right today

May 2 1918 Following the transfusion there was no change in the hemoglobin but the red blood cells increased from 2 624 000 per cu mm to 3 928 000 The patient continued to look much improved by the transfusion The phthalein excretion today was 5 per cent

May 6 1918 The patient was looking very much better and was feeling very well except for occasional headache The blood urea nitrogen now was down to 87 8 mgm in 100 c c The urine contained a small trace of albumin but there was no blood pus or casts

May 9 1918 For the last two or three days the patient was troubled with diplopia This at first was for distant objects but today she was seeing both distant and near objects double *Ophthalmoscopic examination* showed some blurring of the optic discs The patient had some headache during the last few days but no very severe ones Her blood pressure had been increasing somewhat slowly but steadily

June 1 1918 The patient had fairly severe headaches during the last few days and was still troubled with diplopia Phthalein excretion yesterday was 2 per cent and blood urea nitrogen had gone up in the last week from 87 8 mgm to 90 1 mgm The blood pressure had been slowly rising also

June 4 1918 The patient continued to have diplopia although the headache which had been troublesome for the last few days had improved considerably She was able to move her eyes up and down and to the left without seeing double but objects began to blur when they neared the midline to the right of the midline they were seen double and increasingly far apart The right external rectus muscle apparently was the only one seriously affected

June 7 1918 The patient showed left internal strabismus which probably explained the diplopia of the last few days

June 10 1918 The patient s internal strabismus was very much improved She saw double now only very occasionally when looking toward the side General appearance also was much improved She seemed to be doing very well

June 24 1918 The patient was now being allowed up for a short time each day with no bad effects and her time up will be increased every day

June 29 1918 The patient is now up and is walking The blood urea nitrogen was done on June 26 and reported as 64 8 mgm in 100 c c This was a drop of 11 mgm since June 11 The phthalein test done yesterday showed a very slight trace of excre

tion at the end of 2 hours The urinary picture showed no change The patient was looking much better than ever before and was feeling perfectly well

July 2 1918 There had been no change in the patient s condition since the last note She went home today

After leaving the hospital on July 2 she spent 1 month at home resting most of the time The 2 following months she was at a seaside resort While away she had 3 very severe headaches associated with vomiting attacks beside her regular headache of moderate severity about once a week There had been no nausea excepting on the occasions of vomiting For the last month she had been at home, had been resting in bed at least half of the day and had been on a moderately restricted diet She had increased the allowance of vegetables considerably During the time since she left the hospital she had had 2 severe colds at which times her eyes swelled considerably There had been no other edema The bowels had been regular without cathartics Dyspnea on exertion was somewhat more marked than it was at the last entry She particularly noticed this on climbing the hill near her home She had noticed within the past few months considerable twitching of the eyelids but twitching elsewhere in her body had not disturbed her There had also been scotomata before her left eye There had been little of the blurring of vision or diplopia complained of on previous entry The blood urea nitrogen which was in the vicinity of 60 mgm on discharge, was found to have risen to over 90 mgm while she was being followed in the Outdoor Department renal clinic The phthalein excretion had been practically zero The blood pressure had risen also to the vicinity of 200 mm Hg systolic On this account she was sent into the hospital for further observation

Physical Examination November 30 1918 showed a fairly well developed but poorly nourished young woman lying quietly on her back complaining of a severe headache She was conscious and rational *Face* —There was the appearance of edema under the eyes but no pitting was made out None of the edema mentioned before at the previous examinations of the face was present Skin was very pale and pasty Over the chest there were quite markedly dilated veins *Heart* was as it was on last admission *Blood pressure* was systolic 210 mm Hg diastolic 130 mm *Extremities* —*Arms* and *legs* showed occasional twitching motions but not enough to attract the patient s attention There was moderate evidence of wasting no tremor There were two ecchymotic areas the size of a quarter one on the thigh on the left external surface and one on the internal surface of the left ankle said to be bruises but there was no edema

December 10 1918 The patient s condition was distinctly worse now than at previous note Edema of the sides of the neck and cheeks began 3 days ago and progressed rapidly in this respect the condition was similar to that which occurred last April It had been necessary to use sedatives and hypnotics quite freely to keep her from twitching There was quite marked edema of the pharynx so that dyspnea this morning was very troublesome There was also edema in the posterior pharynx pillars being like jelly It seemed for a time this morning as though intubation would be necessary but she breathed easier tonight *Ophthalmoscopic examination* showed that the disc margins were blurred more markedly on the right The vessels were somewhat tortuous There were yellowish areas in both retinae suggestive of an old process A single flame shaped hemorrhage was seen in the right eye none in the left

December 1 1918 The pulse had been rising steadily in the last few days The condition grew definitely worse yesterday Her lungs filled up with bubbling coarse rales which could be heard at a distance She had occasional slight twitching of the hands but no generalized convulsion She died a respiratory death at 10 P M today

Autopsy — Diagnoses chronic nephritis (extreme degree of small granular kidney) cardiac hypertrophy acute myocarditi fibrinous pleuritis early acute vegetative endocarditis arteriosclerosis lobar and bronchopneumonia *Kidneys* were remarkable for their small size and granular appearance They were removed together with the aorta and retroperitoneal tissue The estimated weight of both kidneys was between 60 and 65 gms They were approximately equal in size the left measured 7 cm long × $2\frac{1}{2}$ cm wide × 2 cm The corresponding measurements of the right were 7 × 4 × 2 cm Both were similar in appearance pale and granular The capsules stripped easily leaving uniformly granular surfaces in which the appearance was due to minute nodules 1 to mm in diameter sharply outlined pale reddish yellow in color with intervening retracted deeper red tissue On section the cortices were extremely thin averaging about 2 mm in width pale reddish yellow in color with innumerable fine opaque yellowish radial lines The pyramid were small and light red in color The consistency was fibrous The arteries were prominent but not calcified or rigid In the upper pole of the left kidney involving the cortex and half of one pyramid was a cyst 1 cm in diameter with a smooth lining and containing turbid liquid and many soft pasty but smoothly rounded particles $\frac{1}{2}$ to 1 mm in diameter Both renal arteries were thin walled and free from any lesion and of apparently normal caliber The aortic orifices were remarkably diminished in size surrounded as they were by elevated opaque atheromatous patches The orifice of the right renal artery was puckered but readily admitted a probe having a diameter of 2 mm The inferior renal artery to the left kidney would not admit a probe of this size but did admit freely a probe of 1 mm dimension The superior renal artery had an orifice of the size equal to the right renal artery

Kidney sections showed markedly sclerosed glomeruli and blood vessels with great increase of interstitial connective tissue and atrophy of tubules The sclerosed areas were alternating with those consisting of distended tubules with little if any increase of connective tissue The very striking picture of the sections was a great scarcity of glomeruli and the different pathology they presented As a whole glomeruli could be described as showing hyaline change in their capillary walls which varied from a very slight degree just perceptible to one so pronounced that they appeared merely as a hyaline mass with a few nuclei in it Of those glomeruli looking like a hyaline mass the connecting tubules usually exhibited the most extreme grade of atrophy their lumina being almost or wholly obliterated In those in which the change was not so far advanced there was present in the tuft a varying number of endothelial cells finely vacuolated and their subtending tubules also were less atrophied Not infrequently the tuft had become converted into a compact mass and was covered by a layer of epithelium A few glomeruli looked normal to all appearances The change in blood vessels was mainly limited to arteries which large and small were all affected without exemption In the small arteries the entire wall was thickened while in the large arteries the intima was the only layer thickened or at times the media to a greater or less extent also was involved Reduplication of internal elastic laminae was shown beautifully especially in

the larger arteries Small arteries frequently were obliterated The tubules besides undergoing atrophy as described, were distended showed very much flattened epithelium and had a hyaline content staining either blue or red The connective tissue was infiltrated with many lymphocytes

Summary of Case XVII — A young woman of 23 years without assignable cause unless following scarlet fever at 9 years, at the age of 19 years developed symptoms suggestive of Bright's disease (headache) When examined 4 years later, she had increased blood pressure, albuminuria, a few casts, low specific gravity and strikingly low renal function as shown by much decreased 'phthalein (21 to 18 per cent) and increased blood urea nitrogen (53 to 62 mgm per 100 c c of blood) These conditions persisted from May, 1915 until December, 1918 with strikingly little improvement in renal function at any time In April, 1918 she developed edema of the face and neck, which was marked but persisted only a short time Following this she had uremic manifestations, 'phthalein became a mere trace, and blood urea nitrogen rose to 168 mgm per 100 c c of blood, she had acidosis with a blood CO_2 of 16 mm She recovered from this Again in December 1918 edema of the neck and face recurred, renal function became worse, and she died on December 12, 1918 with moderate uremic manifestations The blood pressure was high most of the time although it fell at times to normal The striking feature in this patient was the very low renal function persisting from May, 1915 to December, 1918 The urine never showed any signs of an active process, and at autopsy the kidneys were small and sclerosed with little functioning renal tissue left This is a type of Bright's disease, in which after extensive renal damage had been produced, probably by a severe acute renal lesion of glomerular type, there was a long latent period with nothing to suggest renal disease and then progress was seemingly very slow, the patient becoming adjusted to a prolonged very low level of renal function lasting for 3½ years of observation

Case XVIII — This case is described in detail on an earlier page as Case XIII in the section headed Subacute and Chronic Hemorrhagic Bright s Disease

The main features of this case can be summarized as follows A young man of 23 entered the hospital with a history indicating that 2 years previously following an attack of influenza an acute hemorrhagic Bright's disease developed The striking feature then were the very numerous red blood cells in his urine with a moderate albuminuria and considerable cylindruria Already phthalein excretion was moderately decreased and blood urea nitrogen slightly increased but blood pressure was not elevated Anemia was very slight Renal function subsequently improved but anemia increased Blood pressure then began to rise and about 4½ to 5 years after onset was 182/108 Red cells continued in the urine but renal function remained only slightly decreased Pneumonia caused death about 6 years after onset of Bright's disease and autopsy showed fairly advanced glo-

merular nephritis Details of thi case will be found under the heading Case XIII on an earlier page

Case XIX — This patient is described in detail on an earlier page as Case XIV in the section headed Subacute and Chronic Hemorrhagic Bright s Disease

The main features of this case can be summarized as follows A man of 34 in December 1920 entered the hospital 3 years after developing acute Bright s disease subsequent to severe tonsillitis Before this time he began to have severe unilateral headaches with nausea and vomiting In the hospital the urine showed many red blood cells and granular casts and had in it considerable albumin Blood pressure was 170/100 'phthalein excretion 30 per cent and blood urea nitrogen 28 mgm per 100 c c In a long stay in the ho pital blood cells decreased in the urine but did not disappear There was no anemia Later red cells and casts increased in the urine and blood pressure began to rise Early in 19 2 headache became severe vision decreased blood pressure rose to high values phthalein de creased blood urea nitrogen rose and anemia became more marked He be came steadily weaker but had no muscle twitchings nor convulsions Azotemia became marked and the patient died 6 years after onset Autopsy showed ad vanced glomerular nephritis Various details of this patient will be found under Case XIV in the section headed Subacute and Chronic Hemorrhagic Bright s Disease

Case XX — This case is described in detail on an earlier page as Case XII in the section headed, Acute Subacute and Chronic Bright s Disease (Nephrotic Type)

The chief features of this patient can be summarized as follows A woman of 50 without any known cause developed edema of her feet which gradually in creased in amount first to disappear overnight later to become constant After about 20 months of this ascites appeared Her urine decreased in amount con tained much albumin many hyaline and granular casts but only very occasionally a rare red blood cell In other words she had a very typical subacute edematous type of Bright s disease the so-called nephrotic syndrome Renal function was very little disturbed For a period of about 5 years she had edema much of the time About 18 years after the beginning of this renal process renal function began to decrease and soon phthalein reached 0 and blood urea nitrogen greatly in creased Also her blood pressure rose About 5 years after the edema first appeared she also had evidence of pyelitis and cystitis which continued but not in a very disturbing way throughout the rest of her life Now there had developed a clinical picture of chronic non-edematous Bright s disease This progressed and caused her death 21 years after the original onset of Bright s disease Autopsy showed small kidneys with the histological lesions of a chronic progressive glom erulonephritis In addition there were well marked vascular lesions probably in large measure in compensation for the atrophy of the kidney which had taken place

Case XXI — A woman of 40 was admitted to the hospital on May 10 1933 P B B H Med No 42984 she died on May 21 1933

This woman had had most of the infectious diseases of childhood, scarlet fever measles chicken pox whooping cough and diphtheria (twice) Also she had pneumonia twice before the age of 7 Twelve years ago at the age of 28 she was told she had high blood pressure Up to the age of 37 3 years ago she had been a healthy vigorous woman She had 5 children and then 2 miscarriages at 6 and 7 months Three years ago she began to be easily exhausted and slightly dyspneic on exertion Then she miscarried and shortly afterward she became blind except for light perception and remained so for 6 months She again became pregnant and miscarried at end of 7 months Since then she has had slight evening edema of ankles frequent severe generalized headaches and urinary frequency with nocturia For 5 months headaches have been very severe with nausea and frequent vomiting and there have been spots before her eyes

Physical Examination May 10 1933 — There was moderate obesity, no pallor but some ecchymoses over lower legs She was slightly dulled in mental reactions Ophthalmoscopic examination showed slight tortuosity and marked caliber changes of arteries with nicking of veins Disc margins were hazy cupping absent There were a few fresh hemorrhages and numerous white patches some in macular region Heart was enlarged to left with short systolic murmurs at apex and aortic area Blood pressure was 265 mm Hg systolic and 165 diastolic Breath was uriniferous Urine had specific gravity 1 008–1 010 considerable albumin many red cells at first, later a moderate number moderate number of white cells at first occasional brown granular and cellular casts later none Phthalein excretion was 0 blood urea nitrogen 90–108–173 mgm per 100 c c. Blood plasma protein was 5 6 gm with albumin 3 8 and globulin 1 6 Blood count was 5 240 000 red cells with leucocytosis of 17 000

Patient steadily went down hill with much nausea retching and vomiting She became increasingly drowsy then semi comatose Four days before death she had a slight convulsion Throughout her hospital stay there were occasional muscle twitchings She had a terminal hyperpyrexia 105° F and Kussmaul breathing She died on May 21 1933

Autopsy — Diagnoses nephritis chronic progressive vascular pyelitis right arterio and arteriolo sclerosis cardiac hypertrophy pancreatic fibrosis with metaplasia of duct epithelium chronic passive congestion of viscera thrombosis of cardiac renal pancreatic and splenic arteries splenic infarcts cholecystitis chronic and cholesterosis of gall bladder bronchopneumonia terminal

Heart weighed 450 gm and showed no macroscopic lesions of valves or myocardium *Kidneys* rt weighed 200 gm left 188 gm Surface in general was smooth and color was reddish with numerous small gray or yellowish gray areas and scattered small hemorrhages Capsule was slightly adherent On section cortex was somewhat and irregularly decreased in thickness with same color as described for the surface In right kidney the pelvis showed diffuse severe hemorrhagico purulent pyelitis Microscopic examination showed marked rather evenly distributed fibrosis with lymphocytic infiltration Arterioles had encroachment on their lumina in various degree up to occlusion by proliferated endothelial cells and their walls in places were hyalinized Glomeruli quite uniformly showed hyalinization of capillaries and some glomeruli were seen as

scars while others had disappeared Tubular epithelium showed granular degeneration and tubules contained numerous granular and hyaline casts The pyelitis already noted was extensive with necrosis of tissue and an inflammatory membrane of polymorphonuclear leucocytes and lymphocyte The former also were found in small number scattered between the tubules throughout the kidney Pathologically the renal lesion could be grouped as progressive vascular nephriti

Summary of Case XXI — This woman who in early life had had very many of the infectious diseases including scarlet fever diphtheria and pneumonia and who had borne 5 healthy children was a vigorous healthy individual up to the age of 37 although at the age of 8 she had been told that he had high blood pressure At the age of 37 she began to be easily exhausted and to have dyspnea Then she had a miscarriage followed by almost complete blindness which lasted for 6 months Again she became pregnant and at 7 months miscarried After this evening ankle edema appeared and she had frequent severe headaches urinary frequency and nocturia followed later by nausea and frequent vomiting

At 40 on May 10 1933 she came to the hospital She was dulled mentally not pale but showed ecchymoses over the lower legs Her breath was uriniferous Her retinae showed arteries with marked caliber changes discs without cupping with hazy margins a few fresh hemorrhages and numerous white patches Her heart was enlarged blood pressure was 265 165 Urine had specific gravity of 1 008–1 010 contained considerable amount of albumin many to moderate number of red blood cells, moderate number of white cells occasionally a few brown granular and epithelial casts Phthalein excretion was 0 blood urea nitrogen 90–108–173 mgm per 100 c c Blood plasma protein was 5 4 gm with albumin 3 8 and globulin 1 6 Blood count was 5 240 000 red cells with 17 000 white cells Patient steadily went down hill had a slight convulsion occasional muscle twitching became increasingly drowsy and died 11 days after coming to the hospital The kidneys were moderately decreased in size 200 gm and 180 gm each There was purulent pyelitis of right kidney There was marked rather evenly distributed fibrosis of the kidneys with lymphocytic infiltration Arterioles showed marked changes with intimal proliferation and hyalinization of their walls Glomeruli quite uniformly showed hyalinization of capillaries some were present only as scars while others had disappeared

Case XXII — A man of 47 was admitted to the hospital on March 1, 1917 P B B H Med No 6297 giving a history of having had inflammatory rheumatism 20 years ago with fever and since then has had about 4 attacks a year Twenty two years ago and 19 years ago he had erysipelas on his face no other history of infectious diseases Twenty five years ago he weighed about 200 pounds and now thinks he weighs about 136 One month ago he had an attack of erysipelas of the face which spread to his chest and then cleared up Three days ago he noticed that his urine was dark colored like coffee and he began to have a rather severe sharp frontal headache which persists

During the past 3 or 4 days he has had chilly sensations but no definite chills His appetite has been poor, and this morning he vomited a considerable amount of brownish fluid For 2 years before admission he had had nocturia once a night

Physical examination showed his face to be rather puffy, a little edematous over the malar bones There was some edema of his palate and the anterior pillars There were scratch marks on his body Heart did not seem enlarged to physical examination and blood pressure was 200 mm Hg systolic 100 diastolic The abdomen was negative there was moderate pitting edema of both lower legs The patient had a fever up to 103° F which fell in the last 3 days to normal and remained normal His urine was smoky in color, had a specific gravity of 1 012 and showed a large trace of albumin, numerous red cells a few white cells a moderate number of granular and cellular casts His blood urea nitrogen was 80 mgm per 100 c c phthalein was 6 per cent A two-hour renal test showed his urine with a fixed specific gravity between 1 010 and 1 013 Hemoglobin was 60 per cent red cell count 4 112 000 which toward the end of his stay in the hospital dropped to hemoglobin 47 per cent and red cell count 3 580 000 Phthalein excretion gradually decreased and reached 20 per cent on May 16th and his blood urea nitrogen increased reaching 110 mgm per 100 c c Ophthalmoscopic examination showed rather blurred disc margins with considerable arteriosclerosis in moderately tortuous arteries some of which seemed imbedded There were no areas of hemorrhage or exudate

The patient s condition seemed to improve, although he continued to complain of headache Then on April 15th he had a generalized convulsion with unconsciousness during which the Babinski became markedly positive in the right foot The rest of the day he was irritable and the next morning he had another convulsion followed by stupor He remained semi stuporous throughout the day erysipelas now developed again in his face and then again he gradually improved his temperature which reached 101° F during the erysipelas returned to normal, and he left the hospital in fairly good condition

He had subsequent admissions as follows July 8, 1919 June 12 1921, February 19 1922 March 20 1925 November 30 1925 and September 27 1928 He died n the hospital September 30 1928 During this time he had continued to show urine with specific gravity from 1 010 to 1 014 with very slight to slight traces of albumin a rare cast and occasional red cells at times increasing to a considerable number Phthalein excretion remained 30 or lower at times being 0 Blood urea nitrogen has been moderately elevated except during his first admission when it was high at a period when he appeared to be having an acute exacerbation of the chronic Bright s disease In 1924 and 1925 ophthalmoscopic examination began to show gray and white or whitish yellow spots in the retina with an increasing degree of sclerosis in the arteries The blood pressure varied always being considerably elevated and often as high as 230 mm Hg systolic and 180 diastolic In the latter part of the course there had been an increasing respiratory difficulty with nocturnal dyspnea From time to time there were exacerbations with redness and local elevation of temperature over his joints On his last admission to the hospital his hemoglobin was 55 per cent red cell count 3 500 000 He became increasingly drowsy and semi-comatose developed twitchings of various muscles over his body gradually became weaker and died on September 30, 1928

Autopsy — Diagnoses nephritis vascular arteriosclerosis generalized including coronary arteries cardiac hypertrophy bronchopneumonia cerebral hemorrhage small cerebral softening old small chronic passive congestion of viscera

The heart weighed 500 grams with some tortuosity of the coronary arteries with evidences of sclerotic plaques but no calcified areas in them The muscle wall was thickened but otherwise looked normal The valves were normal The right kidney was very small measuring 1½ to 1 by 1½ cm The left kidney was considerably larger but still small The cortex of the kidneys was much thinned Scattered through the kidneys were numerous small cysts capsule stripped with great difficulty leaving a granular surface On microscopic examination the kidneys showed an advanced degree of arteriolar change with much increase in connective tissue with areas in which the tubules were atrophied and other areas in which they were hypertrophied All of the glomeruli showed some degree of capillary thrombosis hyalinization and fibrosis The arteries of all sizes even to the smallest including the coronaries showed a most advanced hyalinization and thickening of the walls with splitting of internal elastic lamina into several layers The finer capillaries showed thrombosis and hyalinization the glomeruli showed many points of attachment between the tuft and the capsule The larger blood vessels showed thickening of the media with evidences of fibrosis and hyalinization These kidneys showed typically the lesions of advanced vascular nephritis The right kidney in addition was hypoplastic probably on a congenital basis

Summary of Case XXII — This patient had no history of any form of acute renal lesion and nothing in his history indicated just when the renal process began which caused the very small kidneys Possibly one kidney the right was from birth hypoplastic Hypoplasia of developmental origin may have been present in both kidneys but much less marked of the left than of the right kidney Be that as it may it is evident from the autopsy findings that in both kidneys vascular lesions developed to produce a vascular type of nephritis or an arteriolosclerosis of the kidneys resulting in hypertension and renal insufficiency of the retention type with azotemia In March 1917 he had acute Bright s disease in all probability an acute exacerbation on top of a well developed vascular nephritis From this time on there was slow progression of a renal process which 9 years later caused the death of the patient How long there had existed chronic Bright s disease prior to the acute attack of March 1917 can not be determined from anything in the patient s history

Case XXIII — A male stationary engineer 55 years of age was admitted to the hospital in May 1918 P B B H Med No 8742 and subsequently had 10 admissions until he died in the hospital July 10 1921 His family history is important in that his father had diabetes and died of a cerebral hemorrhage Past history is unimportant except for constant worry and mental strain for years Patient gave a history of dizziness and headache for 10 to 15 years In 1910 he consulted a physician for fainting and was told that he had hypertension In 1914 his systolic pressure was as high as 200 mm Hg He was seen by Dr O Hare in April 1917 for severe headaches They were the usual occipital or frontal early morning headaches Apparently they were not migraine.

Lately the headaches had become very severe The blood pressure was 200 mm Hg, systolic and 120 mm diastolic The urine was negative, and the tests of function were normal (see Table XVII for urine examinations and tests of renal function) In November 1917 the patient was seen again At that time there was no change except that the headaches were less severe and the urine showed a trace of sugar This glycosuria occurred intermittently thereafter

In May 1918 he entered the hospital for the first time for profuse nosebleed which was severe enough to cause him to lose consciousness He stayed in the hospital for 6 days On hospital admission examination showed slight peripheral arteriosclerosis enlarged heart and a blood pressure of 215 mm Hg systolic and 160 mm diastolic. During his stay in the hospital the blood pressure fell to 188 mm systolic and 130 mm, diastolic The urine showed numerous hyaline casts for the first time (see Table XVII) Renal function still was normal although a low normal After leaving the hospital and returning to work the blood pressure rose to 248 mm Hg systolic and 160 mm diastolic Albumin as well as casts were found now in his urine About this time pulsus alternans was first noted

In July 1918 the patient entered the hospital for profuse epistaxis Blood pressure was 216 mm Hg systolic and 142 mm diastolic The urine showed no change Renal function seemed to be falling off slightly (see Table XVII) Physical examination was essentially as before

During the interval between this entry and November, 1918 the patient became more depressed nervous and irritable His memory failed, and he tired easily Physical examination seemed about as before The blood pressure however was slightly higher

In November 1918 after an auto accident the patient entered the hospital for increased nervousness higher blood pressure and slight epistaxis He complained of transient blurring of vision dyspnea on exertion and precordial distress Examination showed that the heart was increasing in size Retinal arteriosclerosis and a few white spots of degeneration were noted in the retinae The urine was essentially the same as before Renal function was essentially normal Pulsus alternans continued to be present After one week in the hospital the patient improved for a time but labor troubles in his plant upset him much Toward the end of December 1918 he had the first of a series of cerebral vascular accidents The first began with a severe headache followed by slight ataxia of the whole left side Two days later he suddenly became unconscious On admission to the hospital within an hour of this accident he was conscious and rational The only abnormality was a suggestion of weakness of the right side of his face and slight ataxia of the left hand Examination showed that the heart was getting larger The blood pressure was lower 202 mm Hg systolic and 134 mm, diastolic Later in the day it dropped to a lower mark 180 mm Hg, systolic and 1 0 diastolic In twenty four hours it had gone up again to 220 mm Hg systolic and 140 diastolic Subsequently during his 2 weeks stay in the hospital it fell to 170 mm Hg systolic and 130 mm diastolic As soon however as he got back to work it rose again as it usually has done The urine showed no change and the renal function was still normal (see Table XVII)

During the early part of 1919 cerebral symptoms increased The patient grew more nervous irritable and sleepless His memory failed and he could not concentrate Later

TABLE XVII

URINE EXAMINATIONS AND TESTS OF RENAL FUNCTION CASE XXIII

Date	24 Hr Amt	Sp Gr	Alb	Casts Hy	Casts Gran	R B C	W B C	Ph	B U N	Wt
1917										
Apr 9	1 860	1 024	0	0	0	0	0	40%		
Apr 23									13 1	
Dec 14	2 290	1 023	0	0	0	0	0			
1918										
May 30	S S	1 022	0	+++	0	0	0			77 4
June 1	S S	1 010	0	+	0	0	0		18 8	
June 3	S S	1 035	0	0	0	+	0	48%		6 2
June 18	S S	1 030	0	+	0	+	0			78 6
July 2										80 2
July 11										80 0
July 12	S S	1 025	+	+	+	+	+			
July 23	620	1 012	++	+	0	0	+	48%	1 6	
July 24	700	1 032	++	+	0	0	+			
Aug 27	S S	1 027	+	+	0	0	+			
Sept 17	S S	1 021	+	+	0	0	0			
Oct 17	S.S	1 020	0	+	+	0	+			
Nov 13	S S	1 016	0	++	0	+	+			
Nov 14	S S		+	+++	+++	0	+			
Nov 16	775	1 0 2	+	+++	+++	0	+++			
Nov 19	S S	1 015	+	+++	+	0	+			
Dec 8	S S	1 020	++	0	0	0	+			
Dec 30	1 250	1 026	+	0	0	0	+			80 4
Dec. 31								64%	12 0	
1919										
Jan 14								50%	13 0	
Jan 21	S S	1 025	+	0			++			
Mar 31								56%	18 0	
Apr 1	2 340	1 021	+	+	0	+	+			
May 23								42%	15 0	
June 28	2 000	1 020	+			+				
July 19	S S		+	+	0	+	+			
Sept 30	S S	1 018	+	++	+	+	+			
Oct 20	S S	1 030	++++	+	0	0	+			
Oct 21									20 0	
Oct 3	S S	1 0 2	+++	+	0	0	+			
Oct 5	S S	1 020	+	0	0	0	0			
Oct 28	S S	1 010	+	+	0	0	+			
Nov 4									18 0	
Nov 8								40%		
Nov 10	S S	1 016	0	+	+	0	+			
Nov 13	S S	1 022	+	+	0	+	+	45%	22 0	
Nov 21	S S	1 026	0	+++	+++	0	+		13 0	
Nov 28								50%	12 0	
Dec 6								45%	11 0	
Dec 2								45%	16 0	
1920										
Feb 24	S S	1 0 6	+	+	0	0	+			
Mar 4	S S	1 024	++	++++	+++	0	+	39%	19 0	
Mar 11									17 0	
June 24	S S	1 004	+	+	0	0	+			82 0
July 29								45%	20 0	75 6
Aug 18								42%	19 0	
Sept 4	S S	1 008	+	+	0	0	+			
Oct 13	S S	1 001	+	0	0	+	+			
Nov 4	S S	1 010	0	0	0	+	0			
Dec. 7									27 0	

URINE EXAMINATIONS AND TESTS OF RENAL FUNCTION CASE XXIII (CONT)

Date	24 Hr Amt	Sp Gr	Alb	Casts Hy	Casts Gran	R B C	W B C	Ph	B U N	Wt
1921										
Jan 12	S S		+	+	0	0	+			73 6
Jan 20	S S	1 006	+	+	0	0	+			
Feb 10	S S	1 008	+	0	0	0	+			
Feb 21	S S	1 010	++	0	+	0	0	42%	35 0	69 0
Mar 3	S S	1 016	+++	++	++	0	0		19 0	67 0
Apr 4	S S		+	+++	0	+	+			
Apr 18	S S	1 008	++	+	0	+	+			
May 4	S S	1 006	+	+	0	+	+		19 0	75 0
May 14	S S	1 010	+	0	0	0	+	40%		
June 18	S S	1 006	++	+	+	+	+		21 0	67 6
June 19									28 0	
June 21	S S	1 018	++	+++	+	0	+			
June 30										67 0
July 7	S S	1 020	+	++	++	+	++	51%	49 0	

Sp Gr = Specific gravity Alb = Albumin Hy = Hyaline Gran = Granular Cell = Cellular R B C = Red Blood cells W B C = White blood cells Ph = Phenolsulphonephthalein excretion in two hours B U N = Blood urea nitrogen in milligrams per 100 c c of blood Bl Cl = Blood chloride in grams per liter of blood Wt = Weight in kilos

† S S = Single specimen
* + = Very slight trace of albumin
++ = Slight trace of albumin
+++ = Trace of albumin
++++ = Large trace of albumin

* + = Rare
++ = Numerous
+++ = Many
++++ = Very many

TWO HOUR TEST OF RENAL FUNCTION CASE XXIII MAY 30 1920

Time	Volume	Sp Gr	NaCl Per Cent	NaCl Gms
7 9 a m	38	1 032	17	06
9 11 a m	50	1 022	33	17
11 a m 1 p m	155	1 016	27	42
1 3 p m	445	1 012	09	40
3 5 p m	9	1 020	18	17
5 7 p m	115	1 020	36	41
7 9 p m	187	1 013	23	43
9 p m 7 a m	654	1 014	21	1 35
Total	1 7 7			3 41

in the year his heart which had up to that time given him only slight distress on exertion began to cause greater disturbance He developed serious paroxysmal nocturnal dyspnea

About the middle of April, 1919 the patient had another cerebral explosion This time it took the form of a left sided epileptiform convulsion This was of short duration and left no residual paralysis Physical examination and urine study (see Table XVII) showed no essential change Retinal examination however showed a marked progression in the vascular lesions *There were now hemorrhages exudate spots of degeneration* and papilledema

During the following summer (1919) the cerebral disease advanced Mental depression was marked His powers of concentration almost vanished Coordination of the movements of both hands was impaired He lost all confidence in himself

On October 19 1919 after a week of increased physical and mental effort he had a complete right-sided hemiplegia The blood pressure was 230 mm Hg systolic and 140 mm diastolic In the course of a week the paralysis of his right side cleared leaving only a slight weakness in his face His speech remained thick and he could not seem to use the proper words His mentality was somewhat clouded In the course of 3 weeks he could speak clearly enough but the words used were often meaningless His aphasia which had been motor and sensory was now only sensory

Examination at this time showed nothing new of note except in the eye grounds These showed a marked increase in the arteriosclerosis with papilledema and edema of the surrounding retina of the left eye He stayed in the hospital almost two months and was discharged considerably improved

In the interval between his discharge and the next entry there was no special change Cerebral symptoms continued The blood pressure remained high and pulsus alternans persisted The urine showed albumin and hyaline and granular casts constantly The renal function showed slight but definite impairment (see Table XVII)

In May 1920 he again entered the hospital because of his mental condition and need of care The heart at this time seemed larger The blood pressure was for him comparatively low 200 mm Hg systolic and 130 mm diastolic The eye grounds had improved The urine was about the same Renal function was almost normal The blood pressure fell as low as 170 mm Hg systolic and 120 mm diastolic At this time the patient stayed in the hospital about three weeks

In August 1920 he re-entered the hospital because of a slight convulsion but stayed only one week His mental condition continued to be very poor but otherwise he seemed in fairly good health

In November 1920 he was admitted for rest and care This time he stayed almost a month There was nothing new of special note at this time except a falling off in renal function

In February 1921 he had three cerebral attacks without paralysis His mental state became worse and worse In May there was another cerebral attack In June 1921 he had a more severe attack with coma or semi coma for almost 2 weeks accompanied by flaccidity of the left arm and leg He then brightened up for a while lapsed into coma again and died 5 days later

Autopsy revealed arteriosclerosis generalized hypertrophy of the heart cysts

of softening in the cerebrum hemorrhages old and recent into the ventricles hemorrhage into the right precentral convolution cyst in each lenticular nucleus bright s disease chronic

Heart weighed 600 grams the muscle was dark red firm and showed no evidence of any lesions The valves were normal The right kidney weighed 100 grams the left 95 Capsules appeared to be thickened but stripped easily leaving a smooth surface Cut surface showed pin point glomeruli and faint reddish striations The larger vessels seemed prominent cortex measured 6 to 7 mm Microscopically although a few glomeruli appeared normal a great many were small with a thickened capillary tuft Others were completely sclerosed and hyalinized Many of the adjacent vessels were sclerosed also There was increase of connective tissue in which were scattered mononuclear cells A few hyaline casts were seen in the straight tubules while the convoluted tubules showed cloudy swelling Pathological diagnosis was chronic progressive nephritis

Summary of Case XXIII — A man of 53 entered the hospital in 1918 with a high blood pressure The history included vascular symptoms that date back 10 to 15 years previously He is known to have had hypertension 8 years previous to this entry or in all for 11 years Actually judging from his history the time probably was from 13 to 18 years From this admission until his death in 1921 he entered the hospital 11 times The first few admissions were for nosebleeds His subsequent admissions were for cerebral vascular accidents or for rest and treatment of his cerebral arteriosclerosis The course of his disease had been predominantly in the cerebral vessels with changes of lesser import in his heart and kidneys His blood pressure had varied tremendously under observation from figures indicating a very moderate increase to extremely high levels, particularly of the diastolic pressure The latter on one occasion was as high as 178 mm Hg Autopsy revealed that as the result of his prolonged vascular disease his kidneys had shrunken and glomeruli and tubules progressively had undergone atrophy with many finally disappearing to justify the diagnosis of chronic vascular nephritis with marked atrophy of the kidneys

Case XXIV — A woman aged 63 was admitted to the hospital P B B H Med No 4315 on March 13 1916 and on five subsequent dates Med Nos 19163 22856 25608 27926 and 31837 dying in the hospital on March 10 1928 12 years after her first admission

This woman had had mumps and scarlet fever many years before her admission in 1916 Two years ago she possibly had typhoid or pneumonia For the past 2 years she had had palpitation increasing dyspnea and swelling of the feet which decreased on resting For 6 months she had had periodically sour eructations relieved by soda At times she had had sharp precordial pain radiating to the shoulder

Physical Examination March 13 1916 — An obese woman of 63 *Heart* showed considerable enlargement to left on percussion with a fairly loud systolic murmur heard best at apex *Blood pressure* was 2,0 mm Hg systolic and 104 diastolic *Lungs* were normal There was no edema *Urine* — Specific gravity ranged from 1 009 to 1 013 with slightest possible trace or no albumin and a few to moderate number of finely and

coarsely granular casts a few white and no red blood cells *Blood* showed 97 per cent hemoglobin and 6 500 white cells *Blood urea nitrogen* was 18 6 mgm. per 100 c.c and *phthalein* excretion 37 per cent *Gastric* analysis showed increased free HCL

She came again to the hospital on July 31 1922 6 years after her first admission now complaining of dizziness staggering inability to think clearly transient blindness dyspnea and edema of legs *Heart* was as before *Blood pressure* was 240/104 *Ophthalmoscopic examination* showed disc margins blurred many white spots no hemorrhages sclerosis of arteries and A V nicking *Urine* was as before Blood showed 4 200 000 red cells 7 800 white hemoglobin 95 per cent urea nitrogen 18 mgm per 100 c c Phthalein excretion was 35 per cent

In the hospital again on Jan 19 1924 her physical examination was much as on her first admission 8 years previously except *ophthalmoscopic examination* now showed more tortuosity of the arteries large white areas hazy disc margins and one small hemorrhage *Blood pressure* was 80/100 *Urine* now showed slight to considerable albumin with sediment as before Blood showed 060 000 red cells 7 000 white cells 95 per cent hemoglobin and urea nitrogen 16 mgm per 100 c c Phthalein excretion was 35 per cent

Her 4th medical hospital admission was on March 27 1925 Her vision was failing more and she was having more palpitation Now she had frontal headaches Various examinations gave results much as on previous admissions *Blood pressure* was 275/100 *Urine* now showed specific gravity ranging from 1 006 to 1 025 with albumin and sediment as before *Blood* showed 3 800 000 red cells 6 500 white cells hemoglobin 70 per cent urea nitrogen 14 mgm per 100 c c Phthalein excretion was 15 to 25 per cent

On Feb 3 1926 she had a fifth medical hospital examination because of increasingly frequent headaches of greater severity *Physical examination* showed no changes *Blood pressure* was 275/115 *Ophthalmoscopic examination* was as before except no hemorrhages were seen In the hospital she had severe angina pectoris once and at times auricular fibrillation *Urine* specific gravity ranged between 1 010 and 1 015 with very little albumin no casts no red cells and numerous white cells *Blood* showed 4 544 000 red cells 4 800 to 9 650 white cells hemoglobin 70 per cent and urea nitrogen 14 mgm per 100 c c Phthalein excretion was 30 per cent

Her last medical hospital admission was on Jan 16 1928 because in general her condition had become worse Her physical examination now was essentially as on her last admission Her *blood pressure* now was 63/120 *Urine* was as before *Blood count* was unchanged Blood urea nitrogen was 20 mgm per 100 c c and phthalein excretion 25 per cent In the hospital mental confusion increased and she developed partial right sided facial paralysis with speech difficulty Blood urea nitrogen increased to 24 39 60 136 mgm per 100 c c and phthalein decreased to only a trace Temperature rose to 102 4 F and she died on March 10 1928

Autopsy diagnoses were nephritis chronic progressive vascular arteriosclerosis generalized cardiac hypertrophy bronchopneumonia pulmonary congestion and edema *Heart* weighed 340 gm with tortuous atheromatous coronary arteries and normal appearing valves and myocardium *Brain* showed a small hemorrhage in the putamen of the lenticular nucleus *Kidneys* weighed 48 and 50 gm with scarred granular surface and much narrowed cortex Microscopically kidneys showed marked thickening and sclerosis of larger and small blood vessels and much scarring of parenchyma Cortex

was markedly sclerosed Many glomeruli were sclerosed, while others showed hypertrophic lobulated tufts some were almost bloodless Tubules were moderately dilated with granular degeneration of their epithelium Scattered small arterioles and glomerular tufts showed acute hyaline degeneration Interstitial tissue was increased

Summary of Case XXIV —A woman of 63 without any previous illness in any etiological relationship to her present illness began to have palpitation, dyspnea and swelling of the feet She had had anginal pain Her blood pressure was found to be much elevated 270/104 Her heart was slightly enlarged Her urine showed a low specific gravity, slightest possible trace of albumin and a moderate number of granular casts 'Phthalein excretion was decreased There was no anemia no azotemia Six years later she had dizziness staggering gait, inability to think clearly and transient blindness in addition to palpitation, dyspnea and edema of the lower legs Cardiac size, blood pressure and urine were as before There was no anemia no nitrogen retention 'Phthalein excretion remained at same moderately decreased level Now ophthalmoscopic examination showed blurred disc margins, sclerosis of arteries and many white spots Two years later findings were the same except that eye ground changes were more marked One year later headaches had begun Now there was moderate anemia, and 'phthalein excretion had decreased from the 35 per cent on first admission to values of 25 per cent One year later headaches were worse and angina pectoris more marked Various findings were as on the previous examination Two years later her general condition had worsened Partial facial paralysis developed Rapidly blood urea nitrogen rose and 'phthalein excretion dropped to a trace She died at the age of 75, 12 years following her first hospital admission, 14 years after her illness began Autopsy showed very moderate heart hypertrophy, marked coronary artery sclerosis Kidneys were small, 48 and 50 gm and fibrosed Many glomeruli were sclerosed tubules were moderately dilated, larger and smaller blood vessels were markedly thickened some arterioles and glomerular capillaries showed hyaline degeneration The kidney lesion was an advanced vascular nephritis Notwithstanding the 12 or more years of marked hypertension the heart was only very moderately hypertrophied

Case XXV —A young girl of 12 was admitted to the hospital on October 16 1941 and died on November 14 1941 P B B H Med No 60 639 Between 1932 and 1934 she was in the Children s Hospital thirteen times because of recurrent *B coli* pyelonephritis with bilateral hydronephrosis and megalo ureters From 1934 to 1941 she was symptomatically well developed normally but had persistent pyuria In July 1941 she developed weakness edema of the legs and face nausea and vomiting She went to the Children s Hospital where she was found to have a blood pressure of 170 mm Hg systolic, 105 diastolic a slightly enlarged heart and abdomen albuminuria pyuria, hemoglobin of 68 per cent and nitrogen retention with hypoproteinemia Following this she felt well for several months except for occasional vomiting but during the past

months her symptoms have recurred she has felt increasingly fatigued and listless she has had some paroxysms of coughing at night but no dyspnea and no urinary symptoms except nocturia once nightly which has been present for a long time For the month prior to her admission to the Peter Bent Brigham Hospital on October 16 1941 she had gone down hill with gradually developing malaise weakness anorexia insomnia and recently drowsiness

Physical Examination — In the hospital she seemed well nourished without distress cheerful and cooperative with slight puffiness of her face and hands The skin was pale and there was a slightly yellowish tinge to arms and axillae and around the navel *Ophthalmoscopic examination showed moderate A V nicking of the vessels* with one or two flame shaped hemorrhages just lateral to the disc on the right The heart did not seem enlarged to percussion but x ray showed fairly marked cardiac enlargement to the right and the left there was a gallop rhythm and a blowing systolic murmur Her blood pressure now was 150 mm Hg systolic 115 diastolic

On October 24th the patient became definitely worse more drowsy had more vomiting and her pulse rate increased to 120 This was followed by some muscle irritability On November 14th she became extremely weak and lethargic She complained of poor vision but ophthalmoscopic examination showed no papillary edema no hemorrhages no exudate She began to have nosebleeds and bleeding gums she rapidly failed and died on November 14th 1941

*Her non protein nitrogen which on October 17th was 205 mgm per 100 c c in*crea ed to 353 on November 10th and 370 on November 12th Her plasma protein on October 17th was 6 1 with albumin 3 4 and globulin 2 7 Her anemia had increased the red cell count dropping nearly to 1 500 000

Autopsy — The diagnoses were pyelonephritis chronic fibrosis of the ureters arteriolar sclerosis generalized cardiac hypertrophy cerebral and pulmonary edema hydrothorax slight hydropericardium slight ascites slight

The *heart* weighed 300 grams and seemed definitely enlarged and dilated There was no pericarditis The myocardium showed no abnormality

Kidneys — The right kidney weighed 30 grams *the left 52 grams There were* numerous adhesions about the kidney There was a scar of an old nephrostomy drainage There were many adhesions on the side of the nephrostomy about the capsule of the kidney involving the perirenal fat The right kidney was much like the left except there was the absence of the scar and adhesions which were present about the left Some of the calices were dilated so that they almost extended to the capsule of the kidney Both ureters were markedly dilated and thickened but there was no evidence of any obstruction Sections of the kidney showed some thickening and fibrosis of the capsule with considerable distortion of the renal architecture with large and small streaky areas of *scarring with marked cellular infiltration involving both cortex and medulla Glomeruli* were practically all markedly altered many were completely sclerosed and hyalinized and others showed *fibrosis some extensively* others only in patches while in some portions the tufts were still delicate The presence of adhesions between the tufts and capsule was a frequent finding There was also considerable peri capsular fibrosis Occasionally some of the less altered glomeruli showed a certain degree of leucocytic infiltration but there were no leucocytes in the capsular space In the scar areas there was

much lymphoid and plasma cell infiltration with some large monocytes and eosinophiles and a liberal scattering of polymorphonuclear leucocytes In the scarred area the tubules were markedly atrophic and small while in some areas they were large hypertrophic with vacuolated granular epithelium somewhat suggestive of a regenerative process Occasionally some of the tubules showed very recent necrosis of the cells Numerous hyaline casts were seen in the tubules as also basophilic casts some with a considerable amount of polymorphonuclear leucocytic and other cellular debris In many areas fibroblastic activity with newly formed capillaries was seen The pelvic epithelium largely had been lost The pelvic connective tissue and peri pelvic fat were fibrosed and showed cellular infiltration as already mentioned The arteries showed only slight sclerotic changes but the arterioles showed more sclerosis

Summary of Case XXV — As a young child of 3 there began a bilateral infection of the kidney causing pyelonephritis hydronephrosis and megalo-ureters From the age of 5 to nearly 12 this young girl was symptomatically well, developed normally but had persisting pyuria Finally she developed weakness, followed later by nausea and vomiting became moderately anemic, had a blood pressure of 170/105 Rapidly she became worse and Oct 16 although still cheerful and well nourished, looked pale and slightly yellowish Her anemia became more marked with red cells falling to 1,500 000 Her heart was enlarged, blood pressure was 150/115 Her blood urea nitrogen increased to reach 205 mgm per 100 c c on Oct 17 353 on Nov 10 and 370 on Nov 12 She died on Nov 14, 1941 For years an inflammatory process had progressively been destroying renal functioning tissue, but the patient adjusted herself to these changes so that for nearly 9 years she was a normally healthy normally developing child, even though renal excretory function was getting less and less effective Only when renal function had become very poor did she show signs of this in her failing health Now her downward course was rapid At autopsy her kidneys showed very few glomeruli and tubules in a structural state to carry on function

Case XXVI — A woman of 32 was admitted to the Peter Bent Brigham Hospital on Nov 25 1931 Med No 4002 and subsequently to the surgical and medical service a total of 7 times until she died Oct 9 1937 6 years after onset of her kidney disease

She developed abdominal pain had an abdominal exploration at another hospital and was told she had an acute pelvic inflammatory process After this she developed pain and soreness in left flank with fever and 2 weeks later came to the Peter Bent Brigham Hospital where on the medical service the left flank was found to be slightly bulging with marked tenderness She had a temperature of 104 4° F pulse of 110 and respiration of 30 *Urine* had specific gravity of 1 010 with sediment loaded with white cells *Blood* showed 3 050 000 red cells 20 200 white cells with 75 per cent polynuclears 50 per cent hemoglobin and 15 4 mgm urea nitrogen per 100 c c Infection in or about left kidney was diagnosed and she was transferred to the surgical service where 150 c c of pus containing *B coli* and staphylococci was drained and diagnosis of left perinephric abscess was made Following operation she had pneumonia Soon she developed acute mid-epigastric pain chills fever and vomiting The left kidney was

explored but no recurrence of perirenal abscess was found She continued to have high fever Blood culture was positive for *B coli* X ray showed bilateral renal calculi On Feb 26 1932 left nephrectomy was done and a septic left kidney with calculi and pyelonephritis was found For some time her blood urea nitrogen was elevated and her course was stormy By April 13 1932 she left hospital much improved In May 1933 she returned to the hospital for removal of calculus from pelvis of right kidney Now she improved greatly and gained 40 pounds in weight Her heart was slightly enlarged blood pressure was 1,0/110 blood showed 4 900 000 red cells 8 800 white cells 80 per cent hemoglobin and 57 mgm urea nitrogen per 100 c c Phthalein excretion was zero Concentration test of urine showed maximal specific gravity of 1 013 and there were very many pus cells in the sediment

In Sept 1935 she had an attack of angina pectoris with numerous recurrences Ophthalmoscopic examination showed increased tortuosity of the arteries and A-V nicking Blood pressure was 175/105 X ray showed linear area of calcification in region of left coronary artery

In March 1937 she was admitted to the medical service of the Peter Bent Brigham Hospital Now her blood pressure was 180/112 Urine had a specific gravity of 1 010 slight trace of albumin and sediment loaded with pus cells Blood showed 3 000 000 red cells 7 600 white cells 65 per cent hemoglobin urea nitrogen 61 mgm per 100 c c total protein 6 gm with albumin 4 2 and globulin 1 8

In April 1937 vomiting began and she became much more fatigued Blood pressure now was 135/85 Anginal attacks were very frequent

On Oct 5 1937 she again was admitted to the medical service Now urine had specific gravity 1 004 and 1 002 and was loaded with pus cells Blood showed 2 400 000 red cells 9 600 white cells hemoglobin 55 per cent urea nitrogen 99 mgm per 100 c c Patient rapidly grew worse blood pressure fell to 80/40 and she died on Oct 9 1937 6 years after onset of renal infection

Autopsy diagnoses were pyelonephritis right nephritis vascular nephrolithiasis right kidney left absent bronchopneumonia bilateral cardiac hypertrophy myocardial infarction old coronary arteriosclerosis marked with calcification left circumflex occluded Heart weighed 360 gm with calcification and occlusion of coronary arteries posterior part of left ventricle showed pale grayish mottled area 3 X 1 cm which histologically proved to be an old infarction

Kidneys left surgically absent right weighed 60 gm and was markedly shrunken nodular and firm and on section normal kidney markings were almost completely obliterated Calices and pelvis showed moderate congestion In a lower calyx was an irregular brown calculus 1 5 X 0 9 cm and from an upper one thick yellow purulent exudate could be expressed Microscopically capsule is irregularly thickened and infiltrated with leucocytes lymphocytes and large mononuclear cells Glomeruli show a great variety of inflammatory and degenerative changes Many are fibrosed Others show increased cellularity and contain leucocytes and lymphocytes Convoluted tubules have indistinct cellular outlines and contain moderate granular debris Many hyaline casts are in straight and collecting tubules Some area in section show necrosis and edema There is a patchy increase of fibrous tissue throughout renal parenchyma Arterioles and larger arteries show marked intimal thickening

Summary of Case XXVI — A woman of 32 in 1931 developed a left sided perinephric abscess She had a temperature of 104 4° F, pulse of 110 and respiration of 30 Urine specific gravity was 1 010 with sediment loaded with pus cells Blood showed 3,050 000 red cells, 20 200 white cells with 75 per cent polynuclears 50 per cent hemoglobin and urea nitrogen 15 4 mgm per 100 c c The perinephric abscess was drained pneumonia developed, fever continued, blood culture showed *B coli* Later x ray showed bilateral renal calculi About 3 months after drainage of left perinephric abscess left kidney was removed, calculi and pyelonephritis were present Blood urea nitrogen remained elevated, but general condition improved greatly One year later calculus was removed from pelvis of right kidney Now her blood pressure was 170/110 blood showed 4,900,000 red cells, 8,800 white cells 80 per cent hemoglobin and 57 mgm urea nitrogen per 100 c c Urine concentration test showed maximum of 1 013, and it contained very many pus cells Phthalein excretion was zero Two years later she began to have angina pectoris at age of 36 Blood pressure was 175/110 Eye grounds showed tortuosity of arteries and A V nicking X ray showed calcification in left coronary artery Two years later she was much worse, blood pressure was 180/112, urine was as before, blood showed 3 000 000 red cells, 7,600 white cells 65 per cent hemoglobin and urea nitrogen 61 mgm per 100 c c Downward course progressed, blood pressure fell progressively reaching 80/40 and she died 6 years after onset of renal infection Autopsy showed calcification and occlusion of coronary arteries with myocardial infarct Left kidney was absent, right weighed 60 gm and was markedly shrunken nodular and fibrosed contained a calculus in one calyx while another contained thick pus Microscopic examination showed connective tissue increase, many glomeruli were fibrosed arterioles and larger arteries showed marked intimal thickening Inflammation had largely destroyed the remaining kidney, but still with decreased renal function indicated by increased blood urea nitrogen and decreased phthalein excretion reasonably good general health long (4 or 5 years) persisted

Onset of Symptoms

Onset of symptoms in many patients is insidious In others the disease can be traced back to an attack of acute Bright's disease, either of hemorrhagic or edematous type or the occurrence of acute pyelonephritis, all with or without intervals of latency of varying duration, each giving a history characteristic of one of these forms of beginning renal disease Frequently, as time goes on the patient notes a loss of weight a lack of strength a decrease in energy and initiative a growing nervousness or irritability, persisting headache, a gradually developing nocturia or some such symptom as the first indication of the existence of a chronic diseased condition Perhaps he takes a rest or undergoes some

symptomatic treatment with temporary disappearance of the symptoms but they shortly recur and grow more aggravated

Digestive disturbances are quite common in these early stages often vague in character a sense of fullness or distention heaviness loss of appetite a furred tongue all temporarily corrected by catharsis the condition often is called biliousness '

One group of cases begins with headache often occipital and matutinal not as a rule very severe but persisting or frequently recurring mistaken for the headache of eye strain or of constipation but when not relieved by properly adjusted glasses or correction of the constipation the cause in Bright s disease is found out Others begin with nervousness increasing irritability lack of ability for mental concentration neuritis or a train of symptoms usually termed neurasthenia

In these various symptoms it is difficult to determine in how far they are due to renal insufficiency or to associated vascular disturbances This is particularly true of those referable to the central nervous system It is quite obvious that with such a variety of symptoms or no symptoms at the onset there is nothing characteristic enough in itself to suggest chronic Bright s disease it is rather that such symptoms not otherwise explicable should arouse the suspicion of and lead to, further search for an underlying Bright s disease

Loss of Weight

The frequent loss of weight in these cases of chronic non-edematous Bright's disease needs emphasis Oftentimes with an associated sallow complexion it arouses the suspicion of an undiscovered neoplasm Loss of appetite distention, abdominal discomfort constipation alternating with diarrhea add probability to that diagnosis and a carcinoma of stomach or intestine is suspected and sought for in vain Occasionally these cases with gastrointestinal symptoms are operated upon before it has been proved that there is no neoplasm causative of the patient s condition This happened with considerable frequency in an earlier day before x ray had made possible a definitive exclusion of gastrointestinal neoplasm

Disturbances of the Alimentary Tract

Many of these patients have a persistent bad taste in the mouth and a coated tongue With the furred tongue there may be a sore mouth and in more advanced stages of Bright s disease frequently this is a very annoying symptom Frequently in advanced Bright s disease a dirty grayish or yellowish membrane forms due to superficial necrosis in various places in the mouth Associated

Summary of Case XXVI — A woman of 32 in 1931 developed a left sided perinephric abscess She had a temperature of 104 4° F, pulse of 110 and respiration of 30 Urine specific gravity was 1 010 with sediment loaded with pus cells Blood showed 3,050,000 red cells, 20 200 white cells with 75 per cent polynuclears, 50 per cent hemoglobin and urea nitrogen 15 4 mgm per 100 c c The perinephric abscess was drained, pneumonia developed, fever continued, blood culture showed *B coli* Later x ray showed bilateral renal calculi About 3 months after drainage of left perinephric abscess left kidney was removed, calculi and pyelonephritis were present Blood urea nitrogen remained elevated, but general condition improved greatly One year later calculus was removed from pelvis of right kidney Now her blood pressure was 170/110 blood showed 4,900,000 red cells, 8,800 white cells 80 per cent hemoglobin and 57 mgm urea nitrogen per 100 c c Urine concentration test showed maximum of 1 013 and it contained very many pus cells Phthalein excretion was zero Two years later she began to have angina pectoris at age of 36 Blood pressure was 175/110 Eye grounds showed tortuosity of arteries and A V nicking X ray showed calcification in left coronary artery Two years later she was much worse blood pressure was 180/112, urine was as before, blood showed 3 000 000 red cells, 7 600 white cells, 65 per cent hemoglobin and urea nitrogen 61 mgm per 100 c c Downward course progressed, blood pressure fell progressively reaching 80/40 and she died 6 years after onset of renal infection Autopsy showed calcification and occlusion of coronary arteries with myocardial infarct Left kidney was absent right weighed 60 gm and was markedly shrunken nodular and fibrosed contained a calculus in one calyx while another contained thick pus Microscopic examination showed connective tissue increase many glomeruli were fibrosed arterioles and larger arteries showed marked intimal thickening Inflammation had largely destroyed the remaining kidney but still with decreased renal function indicated by increased blood urea nitrogen and decreased phthalein excretion reasonably good general health long (4 or 5 years) persisted

Onset of Symptoms

Onset of symptoms in many patients is insidious In others the disease can be traced back to an attack of acute Bright s disease, either of hemorrhagic or edematous type or the occurrence of acute pyelonephritis, all with or without intervals of latency of varying duration each giving a history characteristic of one of these forms of beginning renal disease Frequently, as time goes on, the patient notes a loss of weight a lack of strength a decrease in energy and initiative, a growing nervousness or irritability persisting headache, a gradually developing nocturia or some such symptom as the first indication of the existence of a chronic diseased condition Perhaps he takes a rest or undergoes som-

show changes before they can be made out in large vessels as have been described in Part I To a certain extent these vascular changes are a general result of the diseased condition to a certain extent they are the mechanical result of the maintained high blood pressure The mechanism of this increase in blood pressure and its relation to renal insufficiency and vascular changes have been discussed already in Part I

It is well to remember however that patients with high blood pressure may be encountered whose arteries feel of normal softness are not tortuous and whose walls seem normal The pulse may not be full and bounding or difficult to compress In other words in some patients the physician s finger detects in the digital examination of arteries no suggestion of a high pressure that is present Palpation of the femoral artery against the bone just below Pourpart s ligament gives a better idea of pressure changes than does feeling the radial artery at the wrist but of course the use of a manometer apparatus gives definite knowledge of the blood pressure range

Hemorrhages particularly *epistaxis* are a frequent occurrence in this group of patients due in part to high blood pressure in part to vascular degeneration These nosebleeds often are very copious and difficult to control Not infrequently they are the first evidence of an existing chronic non edematous Bright s disease *Retinal hemorrhage subconjunctival hemorrhage hemorrhage into the internal ear* and *cerebral hemorrhage* are observed often *Renal hemorrhage* may be marked Hemorrhages elsewhere occur but are not so frequent *Hemoptysis* rarely may take place raising the diagnostic problem as to the presence or absence of a complicating pulmonary tuberculosis

The Heart — Changes in the heart sooner or later can be detected in almost all of the patients with chronic non edematous Bright s disease A gradual hypertrophy of the heart take place in most of these cases detectable by the usual physical signs and accompanied by corresponding changes in apex impulse second aortic sound and the cardiac sounds as heard at the apex Just when the hypertrophy begins in each patient often cannot be determined for lesser degrees of thickening of the walls and dilatation of the heart chambers cannot be made out satisfactorily by means of physical examination and x ray measurements may not have been made

Electrocardiography is another means of obtaining information as to the proportionate preponderance of muscle wall on one side or the other of the heart There are changes in the direction and amplitude of the deflections of the ventricular complex *indicating a relative right sided or left sided muscle preponderance* usually the latter Sometimes finding these changes is helpful in diagnosis Moderate degrees of enlargement to the right are the most difficult to determine on physical examination On the other hand a high diaphragm or other causes may lead to displacement of the apex beat suggestive of left sided enlargement

with it superficial ulcerations are common Smears from the necrotic material show a variety of organisms, quite often the fusiform bacilli and spirilla such as are found in Vincent's angina A similar condition may occur in the vagina, colon or rectum

Nausea and vomiting are present very often in patients with chronic Bright's disease of this type They may be very persistent, causing the patient extreme distress and making it almost impossible to feed sufficient nourishment to maintain strength The more marked gastric disturbances usually are regarded as of toxic central origin rather than the result of changes in the mucous membrane of the stomach In later stages chronic passive congestion from cardiac failure brings additional gastrointestinal symptoms Hiccough is common late in the disease often difficult to stop, and it may be an actual important contributing cause to death from exhaustion There may be either constipation or diarrhea With the latter an ulcerative colitis may be found These ulcers in the colon are regarded by some as a manifestation of uremic poisoning or at least directly caused by the Bright's disease in some way Unexplained abdominal pain is not infrequent These gastrointestinal symptoms may lead to a mistaken diagnosis of gall stones etc and cause an ill advised operation again not now so frequently with the x ray available for diagnosis of lesions of the gall bladder and ducts Sometimes intestinal obstruction is simulated I recall one operated on for acute intestinal obstruction with no evidence at the operation of any sort of obstruction being present

With digestive disturbances, especially poor appetite, nausea and vomiting many of these patients have had an inadequate defective diet for a long time and so present evidences of various avitaminoses, which in turn with sore tongue, etc create a vicious cycle of enhanced digestive tract disturbance and resultant further avitaminosis Just how much of the symptoms and signs here under discussion result from vitamin deficiency and how much from the toxemia of renal insufficiency is not certain Both undoubtedly are causative factors

Cardiovascular Disturbances

The greater part of what has already been said on previous pages of Part I about cardiovascular disturbances applies particularly to cases of chronic non edematous Bright's disease Cardiovascular symptoms are very common and sooner or later develop in almost every patient High blood pressure is a nearly constant feature often reaching extremely high figures systolic pressure up to 250 mm of Hg or slightly more rarely over 300, and diastolic pressure correspondingly high With this ordinarily go demonstrable changes in vessels accessible to examination changes that range all the way from slight thickening of artery wall to marked degrees of arteriosclerosis The retinal arteries frequently

the condition which stops inquiry into the final causes and the mechanism operative in these cases

Pericarditis is not infrequent especially in the late stage so-called *pericarditis uremica* Electrocardiograms show changes[163] particularly RS T segment elevations and changes in T wave configuration Friction rubs often are heard Usually appearing late this is not always the case and exacerbations and remissions may be noted with change in or even disappearance of electrocardiographic evidences of pericarditis

Dyspnea

With cardiac failure usually there is breathlessness at first only after exertion later more continuously With it comes cough as would be expected from the passive congestion and bronchitis associated with the cardiac disturbance A most distressing symptom in many patients with chronic Bright s disease and high blood pressure is paroxysmal dyspnea occurring particularly at night This may present itself when there is not much breathlessness at other times Characteristic of it is for the patient to be awakened from sleep by a marked respiratory difficulty in many ways resembling that of a paroxysm of bronchial asthma The attack may persist for a few minutes or up to several hours These dyspneic attacks may simulate closely paroxysms of bronchial asthma Nitroglycerin sometimes gives relief A subcutaneous injection of epinephrin may relieve in the paroxysmal dyspnea of chronic Bright s disease as in bronchial asthma suggesting that spasm of bronchiolar musculature is a factor in the mechanism of both Intravenous aminophyllin often will give relief Cheyne Stokes respiration is encountered often in these patients Frequently it is present only when the patient doses off and it may be quite a factor in hindering sound sleep In some of these patients coffee just before retiring decreases this and so is productive of sleep and not wakefulness The cause of both paroxysmal dyspnea and Cheyne-Stokes respiration appears to be a central toxic one

Skin

Many of the patients with chronic non-edematous Bright s disease have a dry skin often finely scaly from desquamation of superficial epithelium There is a decrease or almost an absence of sweating and the sebaceous glands function less than normal Such a skin is very prone to eczema of various types and local infection takes place easily These changes in the skin may explain why it is often so difficult to induce sweating in chronic Bright s disease Pruritus even when the skin is normal in appearance is a not infrequent and a very annoying symptom An increase in pigmentation often occurs and rarely the patient may

when none exists, and so on the left side there are more errors of commission than on the right, where errors of omission are more common X ray studies, now so general, are very helpful in the study of the heart changes in chronic Bright s disease

It is often the case that a very considerable degree of *high blood pressure* is noted for a long time before there is any considerable evidence of enlargement of the heart In other patients heart enlargement appears early and progresses quickly As time goes on, in many patients the heart becomes very greatly enlarged, both right and left sides being affected The heart muscle sooner or later shows in efficiency in its work Such a condition of affairs we term chronic myocardial insufficiency or chronic non valvular heart disease It is to be remembered that very often the microscope fails to detect any lesion of the heart muscle or any appreciable increase in interstitial tissue in such hearts At this stage evidences of cardiac dilatation are in the forefront with the general body signs of a poor circulation *i e*, edema and chronic passive congestion of the viscera With these changes in the heart there come more and more of the symptoms of cardiac dis ease and with these present it may be difficult to determine the presence of an underlying chronic Bright's disease, which has been the prime cause of the pa tient s condition It is in this stage that cardiac edema confuses the picture of this type of Bright's disease with the one previously described, chronic edematous Bright s disease

The markedly hypertrophied heart of these patients often shows murmurs of various sorts These have been discussed already in Part I

Reduplication and various types of gallop rhythm are noted very frequently in the hearts of these patients Extra systoles cause a frequent irregularity of pulse, and in the later stages auricular flutter and auricular fibrillation very com monly appear The electrocardiogram gives valuable evidence of changes taking place in the heart Pulsus alternans is an accompaniment of the failing heart of some of these patients not infrequently when the pulse is regular in rhythm At other times the first stage of a pulsus alternans is detected only in the beats im mediately following an extra systole

All of these are indications of disturbances of the cardiovascular mechanism but are in no way characteristic of the failing heart of Bright's disease *and in no* sense diagnostic of this condition from any other form of cardiac failure

Precordial discomfort hyperesthesia and at times true anginal pain are met with as in other cardiovascular derangements in which cardiac enlargement with thickening of the coronary arteries is found Coronary occlusion is not infre quent in these patients In many of these patients symptoms from cardiac disturbance almost entirely dominate the picture the condition actually is a cardio-renal disease, and this term might well be used in diagnosis except for the fact that it is apt to be used loosely and lead to a false satisfaction as to knowledge of

related to the vascular lesion and are very little dependent on the toxemia of renal insufficiency[287]. Since in that form of chronic Bright's disease which does not occur in patients primarily hypertensive they develop relatively late in the progression of the disease, their prognostic significance in them is bad and these patients usually live only a few months after the retinopathy has become marked, the average life expectancy in Graham's[371] series being 4.3 months, in Cannaday's and O'Hare's[370] series 6.3 months with 13 months as the longest duration.

The optic disc may be pale or swollen. Such papilledema is frequent in later stages of the disease. With the edema of the optic nerve, if it becomes marked, as sometimes it does, accompanied as it often is by headache and vomiting, the clinical picture of brain tumor with increased intracranial pressure is simulated closely and that mistaken diagnosis at times is made.

Urine

One of the earliest urinary disturbances noted by the patient is an increase in the number of night voidings so that the patient has to rise an increased number of times during the night to empty the bladder. Except in males with enlarged prostate this is an important symptom of chronic non-edematous Bright's disease. Later than this, as a rule, there is an increased frequency of urination during the day. This change seems related to the loss of concentration power with lowering and tendency to fixation of specific gravity of the urine often along with polyuria. *Although ordinarily there is some polyuria, increased frequency may be present* with slight or no increase in 24 hour amount. Even when polyuria exists the individual voiding may be less in amount than normal although with increased frequency the 24 hour total is greater than normal. There is no very satisfactory explanation for the increase in frequency without polyuria. In many patients the increase in frequency and the relative polyuria long remain night symptoms. This increase in amount of night urine is one of the changes of particular importance, causing as it does the nocturia.

The urine is almost always pale in color, of lowered specific gravity and contains only a slight amount of albumin, often only the slightest trace. Specific gravity, as time goes on, tends to become fixed at a constant level for each voiding. Concentration tests show only slight increase in specific gravity, sometimes almost none. The continued low specific gravity, often 1.010 or lower, is a very important evidence of the presence of chronic non-edematous Bright's disease. The inability to concentrate the urine is a reason for the increased amount of urine, since more water must be excreted unless many of the substances usually excreted are to be retained in the blood stream and the body tissues. Casts, as a rule, are not numerous and hyaline casts predominate although all varieties may be found.

present the deep brownish discoloration such as is seen in Addison s disease With an accompanying avitaminosis skin changes characteristic of this appear often

Eyes

Various eye symptoms such as black specks flashes of light, various forms of scotomata dimming of vision, transitory blindness, etc often are complained of Ophthalmoscopic examination is very important, as it frequently detects vascular and retinal changes retinopathy, in a period when symptoms are few The retina permits to the ophthalmoscope almost direct inspection of small arteries and veins with their sub branches Thickening of these either diffuse or patchy, tortuosity temporary or permanent obstruction, hemorrhage, all are easily made out The silvery streaks on arteries the small paler, opaque patches in the course of vessels their relative caliber, especially changes in caliber in the course of the vessel, the narrowing of the vein where the artery crosses, all are important changes indicative of similar vascular lesions elsewhere and particularly suggestive of similar changes in the nearby cerebral vessels Retinal hemorrhages are seen often White or yellowish spots of varying size and distribution are frequent Subconjunctival hemorrhages are not infrequent

In no other form of Bright s disease are retinal lesions, retinopathy, so common Frequency increases as renal disease and hypertension progress In Fishberg and Oppenheimer s[369] series of 55 cases of glomerulonephritis, 19 of which died under observation retinopathy was seen in 41 8 per cent , of the fatal cases 73 7 per cent showed it Cannaday and O'Hare[370] followed ophthalmoscopically 32 patients from the period of no or very slight, retinopathy for as long as 4 years or until 21 had died Of the 21 fatal cases retinopathy had appeared in 82 1 per cent Graham[371] found it in 82 1 per cent of his fatal cases In all of these patients diagnosed as having chronic glomerulonephritis it is important that the retinopathy appeared relatively late in the progression of the disease in contrast to its much earlier appearance in patients commencing with hypertension and developing evidence of renal lesions later Some patients however die from chronic glomerulonephritis with no or only very slight, retinopathy

Not infrequently retinopathy is found when there are few, if any, other signs of a renal lesion The patches of whitish or yellowish color intermingled with hemorrhagic areas in the retina are recognized easily, and there are relatively few conditions to be confused with it These retinal changes are all very significant as indicating that chronic Bright's disease is not merely a kidney disease but a process widely spread and profoundly affecting the body tissues as a whole

Increasingly the view is being taken that there is a close association between these retinal lesions and hypertension, and that in their origin they are closely

related to the vascular lesion and are very little dependent on the toxemia of renal insufficiency[337] Since in that form of chronic Bright s disease which does not occur in patients primarily hypertensive they develop relatively late in the progression of the disease their prognostic significance in them is bad and these patients usually live only a few months after the retinopathy has become marked the average life expectancy in Graham s[371] series being 4 3 months in Cannaday s and O Hare[370] series 6 3 months with 23 months as the longest duration

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Blood usually is absent except during acute exacerbations, or when there are periods of actual hematuria With acute exacerbations the urine picture is that of an acute Bright s disease except for the higher specific gravity usual in that *Periodic hematuria* occurs quite often in this type of Bright s disease Without other change blood appears in the urine This blood may clot in the renal pelvis or ureter, and the passage of clots may cause colic such as is found with renal calculus The cause of this proneness to periodic hematuria is not definitely known By some it is explained by sudden changes in renal arterial pressure causing bleeding within the kidney, by others it is thought to be due to the rupture of varices in the calyces or beneath the epithelium of the renal pelvis, and they report the actual observation of ruptures in dilated venules in these places (Kosumoto[357] Whitney[358] and others) Such hematuria not infrequently leads to mistaken diagnosis of renal or bladder neoplasm, calculus or even tuberculosis Also it should be remembered that the diagnostic error may be in the other direction, certainly a repeated or persisting hematuria merits a thorough x ray and cystoscopic examination to exclude a non nephritic lesion, possibly needing a surgical operation

As a rule, it is fairly easy to distinguish this renal bleeding from an acute Bright s disease with hematuria engrafted on the chronic process by the absence of oliguria by finding a rather small amount of albumin and the presence of a few, chiefly hyaline casts instead of great numbers of cellular and granular casts, such as occur in the acute exacerbation and by a continuance of a lowered specific gravity Furthermore, the renal bleeding is unaccompanied by symptoms such as would be present with the acute exacerbation It is painless, unless the blood clots before being passed, and the passage of the clots cause pain

When passive congestion arises from a coincident cardiac insufficiency in a patient without Bright s disease the urine picture is changed, there is oliguria, darker color, higher specific gravity, increased albumin, more casts and more red cells As at this stage the patients show edema there is some resemblance to the patient with chronic edematous Bright s disease, a resemblance, however, which disappears if digitalis restores circulatory competence

The total solids are decreased in the urine of this type of Bright s disease What is of much interest in relation to the problem of edema is the great reduction that quite often occurs in the output of sodium chloride with and without the development of edema, the latter the so-called dry salt retention This indicates that there is not a necessary causal relation between salt retention and renal edema Nitrogen output usually is normal for some time after a reduction or delay in sodium chloride excretion has taken place later on nitrogen output becomes decreased

The very occasional occurrence of Bence Jones protein in the urine of chronic Bright s disease with hypertension with and without edema has been observed

(Miller and Baetjer[349]) Its significance is not known its cause in chronic Bright s disease is difficult to harmonize with any condition that occurs in diffuse tumors of the bone where there is much more frequent association with Bence-Jones proteinuria Electrophoretic studies of such cases are needed to determine the exact nature of this protein A rare fibrinuria may occur This already has been referred to

Glycosuria slight in amount usually occasional in its appearance, is seen very frequently in patients with chronic non edematous Bright s disease and hypertension especially in those with hypertension This is explained by a hyperglycemia which often reaches a high degree and is quite out of proportion to the glycosuria The condition is the antithesis of renal diabetes in which sugar in considerable quantity appears in the urine when the blood sugar is normal or even sub-normal It is rare for the glycosuria to be a disturbing element in the case and our impression is that few of these patients become advanced diabetics Very moderate restriction of sugar intake as a rule suffices to cause the disappearance of the glycosuria except for occasional traces which seem to do no harm Rigid anti-diabetic dietetic treatment is not only unnecessary but often disadvantageous This statement does not apply to actual diabetes which not uncommonly is associated with Bright s disease In these latter cases appropriate dietetic and insulin treatment of the diabetes gives excellent results

Renal Function Tests

In the early period of the disease concentration tests described in Part I alone show any abnormality In these there is a tendency toward fixation of the specific gravity The night amount of urine is relatively increased with a failure of occurrence of the usual nocturnal increase in concentration It is rather difficult to assign a normal value for night urine as the amount is influenced by the amount of fluid intake and the character of the evening meal An amount at night of over 600 c c however i distinctly suggestive of renal abnormality unles there has been a large fluid intake during the evening All of these slighter changes may be present with no or infrequent albuminuria and cylindruria Later as the Bright s disease progresses specific gravity fluctuates much less night amount of urine is definitely increased specific gravity falls now sodium chloride excretion develops the same departures from normal as have occurred in water excretion Still later nitrogen excretion does the same There are exceptions however to this order of disturbance in water sodium chloride and nitrogen excretion the order may be changed or there may be long intervals between the development of each

In the earlier periods of chronic non-edematous Bright s disease phenolsulfonepthalein excretion is normal as time goes on it gradually decreases in the late

stages it is very slight, or practically none is excreted. Drops in 'phthalein excretion usually accompany periods of circulatory failure, and with improvement in circulation the excretion again rises.

Nitrogenous constituents of the blood increase in much the same relation to the course of the disease as the changes just noted for 'phthalein excretion. Values for total non protein nitrogen roughly parallel those for urea nitrogen and in general a determination of either is equally satisfactory. Extraneous factors influence the level of these nitrogenous substances in the blood, in particular is this true of diet. Protein poor diet causes a fall for example, in the blood non protein nitrogen and when the renal damage is moderate the value returns to a normal level with the patient on such a diet. A diet rich in protein will cause an increase in blood nitrogen from a figure that has been within the normal range on an average diet, when such will not be the case if renal function is normal. Consequently the effects of changes in diet on the values for nitrogenous substances in the blood are both a possible source of error in deductions from these tests and a further means of testing renal function.

Determinations of 'phthalein excretion and of total non protein nitrogen or of urea nitrogen in the blood are of great value in the study of patients with chronic Bright's disease. When the latter still are within normal limits or only a little increased, the urea concentration test is very useful. Determination of other forms of non protein nitrogen in the blood do not add very much to what the preceding determinations tell us. Tests of renal function are discussed on several pages of Part I.

It needs to be emphasized that not infrequently these various tests of renal function reveal serious disturbances in renal function not suggested by other features of the case. Here they have a great diagnostic and prognostic value. Their use in studying patients with chronic Bright's disease gives us much data on which to base an opinion of the value of our methods of management and tells us of the rate of progression of the renal disturbance. It is the trend of repeated tests that has the most value. Used in this manner tests of renal function are of the greatest value in the clinical study and the management of patients with chronic Bright's disease.

Blood Changes

In the later stages of chronic non edematous Bright's disease anemia of some degree is the rule and occasionally it becomes very marked. The anemia is not caused by blood loss which usually is slight or even absent in these patients. Anemia may be marked when there has occurred no known blood loss. Of course, if there is blood loss, an anemia primarily of other cause would be accentuated, and that is observed to happen in these patients. The anemia seems of toxic

origin, and when it is present we find evidences of renal excretory insufficiency such as reduced phthalein excretion or increased non protein nitrogen or urea nitrogen in the blood although the anemia in degree does not run closely parallel to the degree of these changes Indirect evidence points to an inhibition of the hematopoietic activity of the bone marrow and not to any hemolytic process acting on the red cells (Brown and Roth[360] Aubertin and Yacoel[361]

Castle and Minot in their Pathological Physiology and Clinical Description of the Anemias in Oxford Medicine (Vol II Chapt XVI) gave the following The blood picture is suggestive of anemia due to diminished blood production There are few signs of regeneration of the red cells The leucocytes are not always depressed and the platelets usually are normal in number The degree of anemia parallels roughly the degree of nitrogen retention although death may occur from uremia without significant anemia The anemia though usually moderate may be very severe as in 12 cases of nephritis reported by Aubertin and Yacoel[361] in which the average red blood cell count was just above a million per cubic millimeter The lowest value of the color index in an average of 20 cases of chronic glomerular nephritis with anemia given by Brown and Roth[360] was 0 82 The color index usually is slightly above 1 and tends to be higher as the blood count falls In our experience an average red blood cell volume larger than normal usually was found The erythrocytes show little variation in shape but differ somewhat in size Increased reticulocytes and nucleated red blood corpuscles do not appear even with severe anemia With infection the leucocytes show a shift toward immaturity but Schilling states that there is no significant alteration in uncomplicated cases of chronic nephritis Although the skin of the patient often looks yellowish in color the plasma pigments are not increased and the erythrocytes *are not abnormally susceptible to hemolysis by hypotonic salt solutions* The bone marrow has not been adequately studied

Acidosis

Acidosis occurs in varying degree in the majority of patients in the later stages of chronic non-edematous Bright s disease and may be marked enough to cause the usually recognized symptoms of acidosis especially in those patients with evidences of uremia In fact some regard acidosis as one of the features of uremia Slighter degrees of acidosis will be shown by the alkali tolerance test of Sellards In the normal person if 5 grams of sodium bicarbonate are given every 2 hours the urine will become alkaline when 5 to 10 grams have been given in chronic Bright s disease even if only slight acidosis exists, more sodium bicarbonate than this will be needed to make the urine alkaline In the patients with greater acidosis there is decrease in bicarbonate balance in total base in the serum carbon dioxide combining power in the carbon dioxide content of the alveolar air

and in the hydrogen ion concentration of the blood There may be an accumulation of organic acid in these patients Phosphate retention, formerly thought an important factor in acidosis is not so regarded any longer[36-] Some believe that the inability of the damaged kidney to form ammonia may play a part The reduction of base is a very prominent feature in the mechanism of acidosis in chronic Bright's disease These patients are unable to eliminate a highly acid urine according to Peters[363]

Uremia

Uremia occurs with far greater frequency in this than in any other type of Bright s disease Provided the patients do not die from apoplexy, cardiac failure or an intercurrent infectious disease they are practically sure to develop uremia Uremia may be either acute or chronic To uremia are attributed numerous symptoms and findings of advanced chronic non edematous Bright s disease The central nervous system in cases of uremia reveals widespread tissue changes involving both the nerve cells and the parenchymal elements[365] In the acute illness the predominant alteration occurs within the cortical neurons, which reveals an acute change in the nerve cells In the more chronic illness the most striking changes are parenchymal rather than neuronal and consist of focal and perivascular areas of demyelination and necrosis The neurons show both acute and chronic changes in the more chronic illness In many of these patients also there are symptoms and physical changes from organic lesions of the central nervous system of vacular origin so-called encephalopathy or hypertensive encephalopathy discussed in the next section Very often toxic or uremic manifestations are mingled with those caused by various lesions of the nervous system grouped under the term encephalopathy, still further complicating the clinical picture in these patients Uremia has been discussed in Part I largely from the point of view of its cause and mechanism If the reader is not familiar with that, it would be well for him to read those pages at this point

Clinically uremia has been divided into acute uremia and chronic uremia A common factor in uremia is the evidence of retention of renal excretory substances chiefly the non protein nitrogens Without such retention it seems wisest not to regard various symptoms and signs as being uremic in origin If this view is held then there must be in every patient a latent period during which time toxic materials whatever they may be, which are not being excreted from the body are accumulating to a level to cause symptoms and signs Such a latent period of a few days to a week or more is observed in anuria mechanically caused and undoubtedly occurs also in chronic non edematous Bright s disease The major symptoms considered to be evidence of uremia may appear suddenly and gradually disappear this constitutes acute uremia In contrast, and more often,

symptoms appear gradually increase continue or regress without complete disappearance, this is what is meant by chronic uremia

The clinical picture of uremia is a complex of a large number of disturbances some prominent and frequent others less prominent and infrequent These together make up a clinical complex quite easy to recognize while individual factors by themselves readily can lead to erroneous diagnosis Nervous system symptoms are prominent in uremia ranging from headache to coma decreased vision to blindness muscle twitchings to convulsions somnolence to mania with which there is a varying admixture of weakness apathy, loss of weight pruritus anemia stomatitis anorexia hiccough nausea vomiting and diarrhea paroxysmal dyspnea and Cheyne Stokes breathing some of these to be regarded in part or indirectly of nervous system origin others not These changes may be considered of toxic origin, truly uremic

Many patients complain early of easy mental and muscular fatigue They have difficulty in doing accustomed work are unable to concentrate attention get confused have a dull heavy feeling in the head are drowsy and drop off to *sleep to awaken with a start At the same time they are restless and are unable* to sleep for any maintained time so that their nights are filled with sleepless periods Some have periods of excitement talking incoherently screaming and crying out thrashing around possibly becoming maniacal Sooner or later for most of the patients come stupor and final coma

During the entire period headache may be a prominent symptom very disturbing to the patient and difficult to control Usually a dull headache it may be very painful Often the patient has most headache in the morning hours while in others it never lets up except during sleep or under strong sedation There is no type or distribution of headache that is pathognomonic of uremia and it may appear in many forms

Muscle twitching is a frequent symptom far more common than local or generalized convulsions The convulsion of uremia is described in Part I It often shows clinical differences from the convulsion of encephalopathy as will be discussed under that heading

Reflexes usually are active but not often pathological Not uncommonly there is a positive Chvostek facial sign and tetany may occur usually resulting from the vomiting or over ventilation of the uremic

These patients usually have a heavily coated tongue and foul breath not infrequently uriniferous The mucous membrane of the mouth like that of the vagina colon and rectum may show a grayish white membrane with intervening shallow ulcers *In this may be found many bacteria including* the fusiform bacilli and spirilla commonly found in Vincent s angina With this stomatitis salivation often is marked Nausea vomiting and retching generally are *prominent*. The vomitus can contain large amounts of urea when blood urea is much

and in the hydrogen ion concentration of the blood There may be an accumulation of organic acid in these patients Phosphate retention, formerly thought an important factor in acidosis is not so regarded any longer[362] Some believe that the inability of the damaged kidney to form ammonia may play a part The reduction of base is a very prominent feature in the mechanism of acidosis in chronic Bright s disease These patients are unable to eliminate a highly acid urine according to Peters[363]

Uremia

Uremia occurs with far greater frequency in this than in any other type of Bright s disease Provided the patients do not die from apoplexy cardiac failure or an intercurrent infectious disease they are practically sure to develop uremia Uremia may be either acute or chronic To uremia are attributed numerous symptoms and findings of advanced chronic non edematous Bright's disease The central nervous system in cases of uremia reveals widespread tissue changes involving both the nerve cells and the parenchymal elements[365] In the acute illness the predominant alteration occurs within the cortical neurons which reveals an acute change in the nerve cells In the more chronic illness the most striking changes are parenchymal rather than neuronal and consist of focal and perivascular areas of demyelination and necrosis The neurons show both acute and chronic changes in the more chronic illness In many of these patients also there are symptoms and physical changes from organic lesions of the central nervous system of vacular origin so-called encephalopathy or hypertensive encephalopathy discussed in the next section Very often toxic or uremic manifestations are mingled with those caused by various lesions of the nervous system grouped under the term encephalopathy still further complicating the clinical picture in these patients Uremia has been discussed in Part I largely from the point of view of its cause and mechanism If the reader is not familiar with that, it would be well for him to read those pages at this point

Clinically uremia has been divided into acute uremia and chronic uremia A common factor in uremia is the evidence of retention of renal excretory substances chiefly the non protein nitrogens Without such retention it seems wisest not to regard various symptoms and signs as being uremic in origin If this view is held, then there must be in every patient a latent period during which time toxic materials, whatever they may be which are not being excreted from the body are accumulating to a level to cause symptoms and signs Such a latent period of a few days to a week or more is observed in anuria mechanically caused and undoubtedly occurs also in chronic non edematous Bright s disease The major symptoms considered to be evidence of uremia may appear suddenly and gradually disappear this constitutes acute uremia In contrast, and more often,

symptoms appear gradually increase continue or regress without complete disappearance, this is what is meant by chronic uremia

The clinical picture of uremia is a complex of a large number of disturbances some prominent and frequent others less prominent and infrequent These together make up a clinical complex quite easy to recognize while individual factors *by themselves readily can lead to erroneous diagnosis* Nervous system symptoms are prominent in uremia ranging from headache to coma decreased vision to blindness muscle twitchings to convulsions somnolence to mania with which there is a varying admixture of weakness apathy loss of weight pruritus anemia stomatitis anorexia hiccough nausea vomiting and diarrhea paroxysmal dyspnea and Cheyne Stokes breathing some of these to be regarded in part or in directly of nervous system origin others not These changes may be considered of toxic origin truly uremic

Many patients complain early of easy mental and muscular fatigue They have difficulty in doing accustomed work are unable to concentrate attention get confused have a dull heavy feeling in the head are drowsy and drop off to sleep to awaken with a start At the same time they are restless and are unable to sleep for any maintained time so that their nights are filled with sleepless periods *Some have periods of excitement talking incoherently screaming and* crying out thrashing around, possibly becoming maniacal Sooner or later for most of the patients come stupor and final coma

During the entire period headache may be a prominent symptom very disturbing to the patient and difficult to control Usually a dull headache it may *be very painful Often the patient has most headache in the morning hours* while in others it never lets up except during sleep or under strong sedation There is no type or distribution of headache that is pathognomonic of uremia and it may appear in many forms

Muscle twitching is a frequent symptom far more common than local or *generalized convulsions The convulsion of uremia is described in Part I* It often shows clinical differences from the convulsion of encephalopathy as will be discussed under that heading

Reflexes usually are active but not often pathological Not uncommonly there is a positive Chvostek facial sign and tetany may occur usually resulting from the vomiting or over ventilation of the uremic

These patients usually have a heavily coated tongue and foul breath not infrequently urniferous The mucous membrane of the mouth like that of the vagina colon and rectum may show a grayish white membrane with intervening shallow ulcers In this may be found many bacteria including the fusiform bacilli *and spirilla commonly found in Vincent s angina* With this stomatitis salivation often is marked Nausea vomiting and retching generally are prominent The vomitus can contain large amounts of urea when blood urea is much

elevated The saliva too contains it as well as increased non protein nitrogen, these may be quantitated and like in the blood serve as an index of decrease in renal function

Diarrhea may be marked with watery, mucous sometimes purulent, often bloody stools Their ammonia content is high, and this may be causative in part of the lesions of the mucosa underlying the diarrhea The stools also are rich in non protein nitrogen Vomiting and diarrhea eliminate from the body a large amount of these substances

In the uremic dyspnea is frequent partly from the cardiac insufficiency of associated hypertension partly from acidosis, partly from toxic effects on the respiratory center It takes various forms, continuous, paroxysmal Cheyne Stokes or Kussmaul in type The bronchoscope may show throughout accessible mucous membrane exudation somewhat similar to that in the mouth and intestinal tract Myerson[364] has described a grayish, dough like coating in the hypopharynx, larynx, trachea and bronchi

The skin, as a rule is dry, often scaling pruritus is prominent sometimes on a skin entirely normal in appearance except for scratch marks A dull yellowish to brownish yellow appearance of a rather pale skin is encountered frequently This at a glance can suggest the causal chronic Bright s disease, it is quite different from the simple pallor or the lemon tinted pallor of the other anemias, and it hardly would be confused with the pigmentation of Addison's disease myxedema or scleroderma but it may resemble closely the pallor and coloration of the cachexia of malignant neoplasm In a rare patient urea in the sweat may, as it dries crystallize out or precipitate on the skin as a silvery powder, sometimes described as like snow

Anemia sometimes of marked degree, usually is present in uremia, and it may be a very important feature its presence helping to distinguish uremia from the manifestations of encephalopathy

The temperature much more often is subnormal than above normal, but infrequently there is fever rarely hyperpyrexia

Encephalopathy

In chronic non edematous Bright s disease usually as the cases progress blood pressure rises and often reaches high levels In addition various lesions develop in the blood vessels of the kidney and elsewhere in the body as they do in hypertension without Bright s disease i e in essential hypertension With such hypertension and vascular lesions including vascular lesions in the brain, there can be expected essentially the same nervous system symptoms that occur in essential hypertension with essentially normal kidneys symptoms considered to be due to encephalopathy or, as some say, hypertensive encephalopathy In

patients with chronic non-edematous Bright s disease and hypertension nervous system symptoms do occur, when renal function is good enough to make improbable as a cause of them retention of any substance usually excreted in the urine in such cases there seems no possibility of a toxic or uremic etiology for these symptoms In other patients along with hypertension there is renal retention of varying degree and the possibility then exists of nervous system symptoms of both etiologies toxic or uremic and encephalopathic and a clinical picture results more complex than that caused by either one of the two causative factors acting alone In many patients with chronic non-edematous Bright s disease both causes actually are operative but not necessarily in the same degree

The lesions in these patients with encephalopathy or hypertensive encephalopathy are primarily vascular in origin with vascular spasm organic vascular blocking focal or more diffuse cerebral edema and actual hemorrhages Since symptoms may persist for only a short time local vascular spasm is an explanation that is fitting and certain ophthalmoscopic examinations of retinal arteries have given a basis of direct observation for this theory of spasm of retinal arteries and indirectly of spasm of cerebral arteries When symptoms are more persistent an organic lesion of the blood vessel hindering local blood flow including actual thrombosis seems better to explain what happens With blockage of blood flow nutrition of nervous system cells is interfered with whether the blockage is due to spasm or organic lesion and even if this is brief disturbance of the function of vital brain cells would occur In addition one would expect localized edema to develop and this be another form of focal injury With cell injury of any sort reparative changes of focal distribution might ensue, causing a more permanent lesion a gliosis or encephalitis With hypertension and vascular lesions anemia or focal hemorrhages might and do develop With defective circulation small areas of cerebral softening are possible These are the various lesions that are assumed and in some degree observed in the central nervous system of patients with chronic non edematous Bright s disease who have suffered symptoms whose causation lies in the central nervous system

The encephalopathy which is essentially due to focal vascular disturbances but with the possibility secondarily of focal edema hemorrhage softening gliosis in these patients seems responsible for certain symptoms namely headache epileptiform eizures or convulsions drowsiness coma, amaurosis certain paresthesias speech disturbances, psychotic symptoms motor paralyses disturbed reflexes etc. Tonic or clonic convulsions are the most striking symptoms of this encephelopathy but headaches are the most frequent The convulsions may be very violent, they may throw the patient out of bed

With encephalopathy convulsive seizures may be very similar to those of toxic or uremic cause but the ones due to encephalopathy tend to a longer duration and a more frequent association with disturbed reflexes such as a positive Babin

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Diagnosis

Symptoms and signs of chronic non edematous Bright s disease are such that at times confusion of diagnosis may come with such conditions as enlarged prostate *chronic cardiac disease general arteriosclerosis essential hypertension* renal calculus or neoplasm cerebral tumor cerebral hemorrhage epilepsy neurasthenia gastrointestinal disease, pernicious anemia It does not follow from this that there is much difficulty in making the diagnosis in the vast majority of the patients

The urinary frequency and nocturia of chronic non-edematous Bright s disease are symptoms suggestive of *prostatic enlargement* As enlarged prostate causes back pressure on the kidney with albuminuria and depressed renal function it often is difficult to distinguish the prostatic effect from that of a coincident chronic Bright s disease That type of prostatic disturbance in which an enlarged median lobe or other change causes prostatic obstruction without much palpable enlargement of the prostate gland is particularly difficult to distinguish from chronic Bright s disease unless cystoscopic examination is made

Confusion with *chronic cardiac disease* has already been referred to If the lesion in the heart is not easily demonstrated the therapeutic test of the effects of digitalis may be expected to clear up the diagnostic difficulty

As so many patients with chronic non-edematous Bright s disease have *high blood pressure* and *arteriosclerosis* and as both conditions often cause the urinary picture commonly found in this type of chronic Bright s disease it may be very difficult to make out whether the renal lesion is primary or secondary and to determine its significance in the complex. Tests of renal function help here

Those patients of this type with periodic hematuria may resemble patients with *renal calculus* or *neoplasm* X ray study especially with an opaque fluid filling the renal pelvis often is needed to clear up the diagnosis A pyelogram by intravenous injection of a radio-opaque solution or cystoscopy with ureteral catheterization and retrograde pyelogram should be included in the study of such cases That the hematuria of chronic Bright s disease may be and often is unilateral needs to be remembered The patient with renal calculus or neoplasm is less apt to have hypertension so the absence of hypertension is suggestive of the former conditions but this is not always the case

Cerebral tumor cerebral hemorrhage cerebral syphilis cerebral aneurism and *epilepsy* may be confused with chronic non-edematous Bright s disease in those who have uremic attacks or encephalopathy In this connection it should be remembered that a convulsive seizure or suddenly developing coma from what ever cause is accompanied by albuminuria glycosuria and cylindruria Actually often it is not possible to determine the presence or absence of Bright s disease until the seizure is over Mistakes in diagnosis unquestionably are made under

ski sign, motor weakness, thickened speech, etc Also much more frequently do encephalopathic convulsions occur in patients with abnormal eye grounds than is true of the toxic or uremic ones These convulsive seizures often very closely resemble epileptic attacks so much so that they do not require detailed description, but with these the blood pressure, as a rule, rises further, the rise in blood pressure may precede the convulsion

The convulsions may be tonic or clonic lasting from a few seconds to 10 minutes or even longer Very often there are prodromes such as increased headache, increased somnolence or apathy, vomiting restlessness, mental and physical weakness paresthesias such as numbness of a hand or weakness of an arm or leg Except for such prodromes, and these may be absent, the convulsions come suddenly during the patient's normal activity, or while he is asleep An outcry may herald the convulsions Sphincter control usually is lost Pupils generally are dilated and react sluggishly if at all Coma usually accompanies and follows the convulsion, sometimes it begins before the convulsion does Infrequently the patient remains conscious throughout the period of convulsive seizure Amnesia during the period usually is complete Positive Babinski reaction is the rule persisting for a short time after the convulsion Stiff neck and positive Kernig s sign may be present

Instead of, or with, convulsive seizures there may be transient aphasia hemiplegia or monoplegia, amaurosis In some patients such symptoms and signs may persist

Delirium is a frequent accompaniment of the seizures or more often a sequence It consists of restlessness wild talking and gesticulating Visual or auditory hallucinations may occur

The previous paragraphs are sufficient to give a general idea of the symptoms considered to be due to encephalopathy With the focal nature of the cerebral disturbance and the variation in what actually happens in the circulation of the brain, it is obvious that there may be a great variety in symptoms and signs of this origin

In individual patients a general type of disturbance may be expected, but much variation in the clinical picture should not be a surprise It is the accompaniments and followings of the seizure rather than the type of convulsion which indicate that the phenomena here described are to be considered to be of encephalopathic rather than uremic origin The evidence of encephalopathic origin, however can be considered satisfactorily complete only in those patients in whom renal function is good enough for phthalein excretion and nitrogen retention to be normal or only moderately abnormal When the latter is not the situation what happens may be encephalopathic in origin, but it could be, in part at least, uremic in origin An attempt to separate the two, as has been done in these two sections seems of usefulness to the clinician

that the patient might live six months Their diagnosis was correct their prognosis missed the mark by some 30 years the patient had chronic Bright s disease and died in uremia after a life of only very moderate invalidism Such an error indicates either that their basis of estimating prognosis was *very inadequate or* that there are remarkable variations that occur in the progression of the disease in individual patients There is little doubt but that both factors prevailed then and that both still hold to a very considerable degree notwithstanding the great progress we have made in recent years in methods of measuring renal function It is a fact that in chronic Bright s disease without edema renal function may be at a very low level without the general condition of the patient or the ordinary methods of examining the urine giving any indication of this Furthermore it is true that at even a very low level of renal function progression of the process may practically cease as shown by some reported cases of O Hare[364] and the patients remain in statu quo for a long time On the other hand progress may be steady and duration relatively short

It follows from the preceding that methods of measuring renal function are of very great value in estimating prognosis in this type of patient Determinations of phenolsulfonephthalein excretion and of levels of total non protein nitrogen or urea *nitrogen in the blood are of the greatest aid* Still it must be remembered that not single tests but tests repeated at intervals are necessary to form an idea of the progression of the proces a very important factor Various extraneous factors such as circulatory disturbances diet etc may play a very considerable part in causing renal function as measured by these tests to vary and these need to be taken into consideration and either allowed for or corrected before drawing conclusions as to prognosis

Finally it needs to be recognized that intercurrent infections and cardiovascular disturbances or cerebral hemorrhage frequently have more to do with causing death in this group than does the renal condition with its defective function As prognosis based on estimation of renal function concerns alone the probability as to death from renal insufficiency allowance must be made for these other factors before stating the probable duration of life in this type of patient This is not the proper place to discuss methods of estimating prognosis in cardiovascular disease but it is evident that in chronic Bright s disease without edema in which cardiovascular disturbances are prominent these need to be estimated as to their prognostic significance by every available method before forming a judgment as to prognosis in the given patient

A persistingly low phthalein output and high blood urea nitrogen in a patient with *chronic Bright s disease mean a poor prognosis In some* patients with these there are a very few evidences in the urine in the way of cells and casts of any active degenerative changes going on in the kidney *and these* individuals may at times remain for several years in essentially the same condition They

these circumstances in both directions Frequently lumbar puncture gives data of great help in diagnosis in this group, finding a positive Wassermann reaction, xanthochromia, red cells not the result of the trauma of puncture or an increased amount of protein or increased white cell count in the spinal fluid point to a non renal cause of the symptoms In cerebral tumor a blood pressure above 160 mm systolic is unusual, and secondary anemia is rare

As far as *neurasthenia* and *psychoneurosis* are concerned the point in diagnosis is not to overlook the usual signs of chronic Bright's disease because symptoms are of such a nature as to suggest neurasthenia or psychoneurosis There is a tendency in seeing these nervous individuals to be satisfied with a snap diagnosis and not really give the patient that careful sort of study that might be expected to reveal an underlying organic disease Such patients not infrequently suffer from having a psychological or psychoanalytical study with the omission of most of the ordinary physical examination, or when the latter is made it is done in too cursory a fashion or by one better versed in the study of the mind than of the body i e by a neurologist, who is but a poorly trained diagnostician of general bodily ills unfortunately proportionately about as many neurologists belong to that group as do general internists to the group who know almost nothing of neurology and neurological methods

Gastrointestinal symptoms in chronic non edematous Bright's disease but too often lead to the mistaken diagnosis of *acute* or *chronic indigestion*, *gastric ulcer* or *cancer gallstones*, etc Chronic indigestion may be long treated, because it is a prominent symptom and the physician not even suspect the causal Bright's disease Various mistaken diagnoses of gallstones, chronic gastric ulcer, chronic appendicitis intestinal obstruction and intestinal neoplasm may lead to operation, when the symptoms merely accompany chronic Bright's disease I have treated patients with chronic Bright s disease previously operated on for each one of this group of wrong diagnoses

Pernicious anemia with its sallow pallor its gastrointestinal symptoms, slight pitting edema of the ankles and its albuminuria with a few casts and low renal function as measured by the two-hour renal test (Christian) may simulate chronic Bright's disease very closely, and the true diagnosis only be made when the patient is studied with the possibility of this condition in mind

Prognosis

Prognosis for duration of life is better in the non edematous than in the edematous type of chronic Bright s disease Eventually the chronic Bright s disease or its associated cardiovascular disturbance kills, but the duration of the disease often is one of years I know of a case in this group in which two eminent consultants made a diagnosis of chronic Bright's disease and expressed the opinion

turbances dyspnea irregular respiration changes in vision should be noted and not considered of trivial significance The careful physician watching his patient can after all form a very good idea as to progression of events in the course of the disease *I would emphasize that no method of measuring renal function justifies failure to note carefully variations in the patient to be made out by the eye tempered in its observations by common sense and a knowledge of Bright s disease built upon a basis of carefully observed cases* Very often not always the unexpected change found in renal function is unexpected in inverse ratio to the attention the physician has been giving his patient

TREATMENT

Treatment is in large part a matter of regulating general hygiene with a view to reducing to a minimum the incidence of infection and affording as far as is possible functional rest to the kidney and physical and mental relaxation to the patient The significance of rest for the kidney as important in the treatment of Bright s disease long has been recognized and has support in many clinical studies of the disease in man and in observations made on animals with experimentally produced renal lesions The studies of Addis and his associates have emphasized this particularly well[457, 458] To keep the patient in good general condition and to reduce strain is the goal sought by most methods of treatment

There is little to be done in the way of direct treatment of the renal condition Early recognition of the disease is of help in enabling us to guard the patient as much as po sible against infections and to prevent excesses in eating drinking and the various activities of life There is no doubt but that patients diagnosed early who live careful lives have a prolonged period of rational life with this idea Osler wrote on the advantages of finding a little albumin and a few hyaline casts in the urine On the other hand we needs must acknowledge the impotence of much lauded preventive medicine when we are dealing with chronic Bright s disease

Diet

Strong alcoholic drinks should be interdicted to the patient with non-edematous Bright s disease light wines in moderation do no harm a moderate use of tobacco may be continued by almo t all Over eating should be stopped just as zealously as the use of alcohol Diet would seem to be a very important feature of the treatment but as to the real effects of the long continued use of the various elements of the average diet we have a most surprising lack of knowledge Our dietary management is almost entirely empiric because it is to be applied over a long time in a chronic condition when our accurate observations are few and

are however distinct exceptions to the general rule that if 'phthalein excretion remains below 10 per cent in 2 hours and urea nitrogen above 40 mgm per 100 c c of blood the duration of life will be less than one year Such low values may be found by reason of a temporary cardiac disturbance a dietary indiscretion or an acute exacerbation of renal process and improve later, obviously then the prognostic significance is changed, prognosis is not so serious as these tests at that given time otherwise would indicate

Ophthalmoscopic examinations are of much prognostic importance Retinitis in this group is of very bad omen, most of the patients showing it dying within the year Retinal hemorrhages are by no means of such serious import Ophthalmoscopic examination gives us accurate information as to a group of small blood vessels intimately associated with the cerebral arteries and affords us our best available index of the condition of the cerebral vessels and the existence of encephalopathy From the condition of the retinal blood vessels we can form some idea as to the probability of cerebral hemorrhage, often the terminal event in the chronic nephritic without edema

Ordinary methods of urine examination especially variations in albumin content are of relatively little help in prognosis Very frequent examinations of this kind probably are best omitted as they serve to depress the patients unduly if their result is reported to them It is highly inadvisable to allow the patient to examine his own urine for albumin Albuminuria is a very poor index of what diet should be allowed the patient Variations in cells and casts are of greater significance but on the whole are more a source of error than of aid in the management of the patient with the probable exception of the appearance of red blood cells

Repeated measurements of blood pressure are of little aid Particularly as at the present time blood pressure is such a matter of parlor and other polite conversation and as it is difficult to measure it without your patient knowing the result I have come to the opinion that it is best to omit the repeated estimation of blood pressure Blood pressure estimates are of diagnostic help occasional repetitions aid us but in general knowledge of the height of the blood pressure from day to day is of no value in the management of the case and its significance is best made out from symptoms and signs of cardiac disturbance obtained from the general examination of the patient So I would say do not make a daily or a regularly repeated blood pressure determination in the patient with chronic Bright's disease that you are treating from time to time blood pressure measurements should be included in the general physical examination of your patient without undue emphasis to the patient of any particular significance attached to that phase of your examination

Changes in the patient s symptoms often suggest an impending uremia or the seizure of encephalopathy Increased nervousness or headache digestive dis-

of protein and the necessary vitamins As a basis of such a diet at the Peter Bent Brigham Hospital we set as a standard not to be exceeded in protein value for mild to moderately marked chronic Bright s disease a daily intake of 75 grams of protein and a carbohydrate and fat moiety to make up about 2 000 calories This has been termed standard nephritic diet and may be summarized as follows

STANDARD NEPHRITIC DIET

Food	*Amount*	*Protein*	*Fat*	*Carbohydrate*	*Calories*
Milk	400 c c	13 2 gms.	16 0 gms.	0 0 gms.	276 8
Cream	60 c c	1 3 gms.	24 0 gms.	1 8 gms	228 4
Olive oil	20 c.c		20 0 gms.		180 0
Butter	45 gms.	0 4 gms.	38 2 gms.		345 4
2 Eggs	100 gms.	13 4 gms.	10 5 gms.		148 1
Sugar	25 gms.			25 0 gms.	100 0
Cereal	150 gms.	3 3 gms.	0 4 gms.	17 6 gms	87 2
Bread	60 gms.	5 5 gms.	0 7 gms.	31 6 gms.	154 7
Macaroni	100 gms.	3 0 gms.	1 5 gms.	15 8 gms.	88 7
Vegetable	300 gms.	6 0 gms.		30 0 gms	144 0
Cocoa	5 gms.	1 0 gms.	1 4 gms.	1 8 gms.	23 8
Meat	150 gms.	28 5 gms.	18 0 gms.		6 0
Totals		75 6 gms	130 7 gms	143 6 gms.	2 053 1

If this is prepared without adding sodium chloride it will rarely exceed a two-gram value of that salt for 24 hours and to this may be added when the meals are served enough sodium chloride to give an approximate total of three to five grams of sodium chloride per day as determined for the patient as being the desirable salt intake This salt had best be placed on the patient s tray to be used as taste dictates Coffee tea cocoa lemonade orangeade water are added in proportion as is needed to make up the 24 hour intake of fluid regarded as desirable for the patient On such a basis very good daily menus may be constructed as the following example shows

Breakfast

1 orange
150 gms cream of wheat
(20 c c. cream)
1 egg scrambled
20 gms of toast
15 gms of butter
150 c.c. coffee
(cream 20 c c)
(sugar 10 gms.)
(milk, 25 c c)

Forenoon

200 c c. milk

Dinner

100 c.c milk soup
75 gm roast beef
100 gms potato
100 gms carrot
0 gms bread
15 c c. butter
Custard
(milk, 100 c c)
(sugar 10 gm)
(1 egg)
150 c c tea
(milk 25 c.c)
(sugar 5 gm)

Afternoon

150 c c orange or lemon ade
(sugar 5 gm)

Supper

50 gms chicken
100 gm spinach
100 gms baked apple
(sugar 5 gms)
(cream 0 c c)
150 c c. tea
(sugar 10 gms)
(milk, 25 c c.)
0 gm bread
15 gms butter

almost entirely limited to very short periods of time There is a great need for investigation of the effects of long continued diets in patients with chronic Bright's disease

As for diets so for fluids There is no satisfactory work on which to base a view as to how much fluid is best for chronic Bright's disease without edema In acute Bright's disease and in some forms of chronic we at times see that an increase in water intake is followed by a fall instead of an increase in urine amount From this we argue that increased fluid in its excretion causes increased work on the kidney and so may do injury to a kidney already working nearly at the level of its maximal ability to work In acute experimental nephritis diuretics, including water cause a shortening of the period of life of the animal (Christian and O Hare[367] and Walker and Dawson[368]) Increase in water intake frequently increases edema and decreases urine flow in cardiac cases and in patients with Bright s disease of the edematous type Such observations are the cause of the opinion, quite generally held that an excessive fluid intake is undesirable for Bright s disease of any type However, does this justify any opinion as to the optimum of fluid intake to be persisted in day after day for the long period of duration of disease in chronic Bright's disease without edema? Does it justify discarding the claims of good from a large water intake especially as followed at certain spas? In spas is it the water or its mineral content that is beneficial? These are questions that we should put honestly to ourselves and seek to answer by carefully planned observations of patients and their renal function continued over long periods of time with various diets and varying fluid intakes Until this is done we need to recognize fully the empiricism of our advice as to diet and fluid intake for the chronic nephritic without edema

At the present time on the basis of such information as we have, it seems justified to advise the following in regard to dieting the patient with chronic non edematous Bright s disease Fluid intake should be moderate, ranging between 1,200 c c and 1 800 c c per day increased when sweating is considerable or marked this latter applies both to the natural sweating varying with atmospheric temperature and moisture and to artificially induced sweating the latter infrequently practiced in the present period of time Fluid intake should be chiefly good water milk lemonade orangeade and a moderate amount of tea, cocoa and coffee For many tea and coffee should be omitted or caffeine free forms used The patient s natural thirst is a good index as to the amount of fluid to be given after the patient has had some guidance by a period of actual measuring of the fluid intake

In the same general sense diet should be established on the principle of moderately reducing the intake of protein and extractives and of sodium chloride substances which seem to cause most work on the kidney in their excretion and at the same time arranging so that the diet is adequate both in calories and in variety

have a very considerable effect, later the effects usually are not very marked still these focal infections should be treated whenever found It is to be remembered that not every rarefaction revealed by x ray at a tooth root means a focus of septic absorption and that not every tonsil which is not normal is a source of trouble Teeth but too often are extracted uselessly tonsillectomy particularly in adults is an operation not to be undertaken lightly and the operation may be far more injurious than the assumed focus of infection Rare good judgment is needed in diagnosing and determining the effect of focal infections of all sorts before advice as to their treatment is given I am of the opinion that today by many, much harm is being done by the radical treatment of supposed foci of infection, it is a wrong attitude to take when one says having found no other cause I will remove the tonsils even if careful examination reveals no actual disease or I will have several teeth extracted because a slight x ray rarefaction may indicate a droplet of pus Certainly the exercise of common sense is needed in this matter

Climate and Exercise

A warm equable climate free of great extremes of temperature and moisture suitable for a daily out-of-doors existence is best for the patient with chronic Bright s disease High altitudes are undesirable as is a low moist debilitating coastal region Moderate open air exercise is of great help Golf is a most excellent sport for these patients until the advanced stage of the condition compels almost complete rest In-door exercises sun and various light baths different forms of moderate hydrotherapy are helpful adjuvants especially in colder climates A let-down in business strain is very desirable stopping all business activity is rarely an advantage When first recognized the effect of a reasonably prolonged vacation serves as a most admirable guide as to the probable effect on the individual of subsequent reduction of various sorts in his activities In this matter a very individualistic management is needed

Treatment of Special Features

Uremia —When renal function as measured by phthalein excretion and determinations of blood non protein nitrogens finally falls to levels low enough to bring about the early phases of various toxic phenomena then the difficulties of treatment are vastly enhanced When uremia actually is present the problem of therapy has become very difficult

In the early stage of these developments very often lowering the protein intake to 25 or 20 grams a day as already described will reduce the blood levels of non protein nitrogen and improve the patient With diet at this level of protein its

To such diets should be added various green vegetables, fruits and salads so that an adequate intake of vitamins will be afforded in addition to those in the foods already listed, if these increase total calories, that is no objection to their inclusion in the diet As in other chronic diseases in which defective appetite may be prominent, and this is almost always true to some to marked degree in the more advanced stages of chronic non edematous Bright's disease, getting the patient to take steadily a diet completely adequate in all respects often is difficult, and various forms and degrees of vitamin deficiency develop, with the result that many of these patients show the symptoms and signs of avitaminosis These should be looked for periodically in each patient and, when found receive prompt treatment with purified vitamin preparations, given parenterally, when there is evidence of deficient ingestion and absorption or increased loss by reason of diarrhea otherwise they should be given by mouth Our present ability to recognize avitaminoses and supply those that are deficient has greatly improved the condition of many of the patients with chronic Bright s disease

If from changes in renal function or in the patient's condition it is evident that the renal process is a marked one, the protein level in the diet is reduced, as needs be down to the level of 25 grams per day a so-called low protein diet as already described on a previous page If there is reason to know that sodium chloride is excreted with great difficulty, it in turn is reduced Patients quite readily accustom themselves to using only small amounts of salt with their food, particularly when the amount is gradually reduced and flavor is supplied by fruit jellies.

Spices, peppers and all condiments should be forbidden to these patients As these are left out and salt is reduced in amount especial care must be taken in serving the meals and by frequent changes in their content to make them as appetizing as possible When the patient's appetite flags the question should be raised at once, is this due to incipient nausea of beginning uremia or to the kind of diet furnished? If the former as indicated by evidences of decreasing renal function treatment should be directed to that condition If on the other hand, the loss of appetite comes from other causes the patient should have more time out of doors more exercise increasing this with caution, and a change in diet At this time it is distinctly more worth while in fairly wide limits to stimulate the patient s appetite with food he may crave than to adhere to a diet restricted in protein and in other ways It would seem that the use of amino acids, already discussed in the section on treatment of the edematous form of Bright's disease, might have a good use also in these patients

Foci of Infection

Removal of foci of infection is an obvious duty in managing the patient with Bright's disease including the chronic varieties In the early stage this may

have a very considerable effect later the effects usually are not very marked still these focal infections should be treated whenever found It is to be remembered that not every rarefaction revealed by x ray at a tooth root means a focus of septic absorption, and that not every tonsil which is not normal is a source of trouble Teeth but too often are extracted uselessly tonsillectomy particularly in adults is an operation not to be undertaken lightly and the operation may be far more injurious than the assumed focus of infection Rare good judgment is needed in diagnosing and determining the effect of focal infections of all sorts before advice as to their treatment is given I am of the opinion that today by many much harm is being done by the radical treatment of supposed foci of infection it is a wrong attitude to take when one says having found no other cause I will remove the tonsils even if careful examination reveals no actual disease or I will have several teeth extracted because a slight x ray rarefaction may indicate a droplet of pus Certainly the exercise of common sense is needed in this matter

Climate and Exercise

A warm equable climate free of great extremes of temperature and moisture suitable for a daily out of-doors existence is best for the patient with chronic Bright s disease High altitudes are undesirable as is a low moist debilitating coastal region Moderate open air exercise is of great help Golf is a most excellent sport for these patients until the advanced stage of the condition compels almost complete rest In-door exercises sun and various light baths different forms of moderate hydrotherapy are helpful adjuvants especially in colder climates A let-down in business strain is very desirable stopping all business activity is rarely an advantage When first recognized the effect of a reasonably prolonged vacation serves as a most admirable guide as to the probable effect on the individual of subsequent reduction of various sorts in his activities In this matter a very individualistic management is needed

Treatment of Special Features

Uremia —When renal function as measured by phthalein excretion and determinations of blood non protein nitrogens finally falls to levels low enough to bring about the early phases of various toxic phenomena then the difficulties of treatment are vastly enhanced When uremia actually is present the problem of therapy has become very difficult

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carbohydrate, fat and vitamin content need to be increased, if the patient is able to take such supplements to his diet. An increased fluid intake now should be instituted also; sometimes it is helpful, it may, however, bring about some cardiac decompensation and this should be watched for and treated with digitalis, if it becomes evident. It is to be remembered that with protein reduction in diet we create the factors which are likely to bring about lowering of the plasma protein levels and to cause anemia. If there is any evidence of these, now is the time to use transfusions of plasma and whole blood, the latter if anemia exists. By these measures a temporary renal insufficiency, if such it is and such do occur in these patients, can be bridged over and the final progressive fall in renal function postponed.

Other than renal routes for the elimination of the retained toxic substances of uremia theoretically are available. These are 1) methods of vividiffusion, 2) methods for tube irrigating the bowel and 3) methods for peritoneal irrigation. Vividiffusion involves the creation of an artificial dializing membrane through which the animal's or the patient's blood is made to flow after the use of heparin to prevent clotting. Such an apparatus was described in 1914 by Abel, Rowntree and Turner[452] but did not prove practical for man. Recently somewhat similar methods have been devised and applied to some uremic patients with encouraging results[453, 454]. Tube irrigation of the bowel with fluids of proper electrolyte composition is entirely possible and will remove a certain amount of retained toxic products[455]; in use the amount so removed has not been great enough to have any very great clinical effect[436], but different arrangement of the drainage apparatus might give better results[491]. Peritoneal irrigation gives greater promise[436, 437], and successful cases have been reported[454]. The content of the fluid for peritoneal irrigation is such as to avoid depleting the plasma of its electrolytes and glucose and to prevent acidosis. Fine and his associates[436, 456] have used mammalian Tyrode's solution with added glucose; to this is added penicillin and streptomycin for bacteriostasis on possible contaminating bacteria and heparin to prevent fibrin deposition in the peritoneum. Inlet and outlet tubes are introduced into the peritoneal cavity through incisions into the abdominal wall, the outlet tube is a stainless steel so-called sump drain. The sterile solution in very large amount (25 to 30 liters per day) is run by gravity into the peritoneal cavity through the inlet tube and is drawn out through the outlet tube by a continuous suction system. In a patient[436] in which peritoneal drainage flow averaged 25 c.c. per minute an average of 12 to 20 gm. of urea were removed per 24 hours and blood urea nitrogen fell in 6 days from 72.7 mgm. per 100 c.c. to 37.8. Then urine flow which had been greatly reduced returned toward normal, and the patient's uremic manifestations disappeared.

Such observations as these indicate that the toxic condition which we call uremia, may be cleared by continued peritoneal irrigation with a fluid "designed

to restore and maintain the normal electrolyte composition of the plasma and the extracellular fluid, to correct acidosis to prevent depletion of glucose and to minimize fibrin formation and the development of infection of the dialyzing membrane [1436] The peritoneum serves as a dialyzing membrane, through which the toxic material causative of uremic manifestations is removed The amount of urea so removed and the resultant decrease in blood non protein or urea nitrogen serve as an index of the efficiency of the method as well as do the changes in the patient s clinical condition This method makes possible to tide over a uremic condition until kidney function again becomes effectively efficient Obviously it can not be used to replace renal function beyond a few days during which the kidney will have time to recover from a temporary type of lesion which has reduced greatly its function In the case reported by Fine and associates[436] this was caused by sulfonamide intoxication other kidney lesions can cause an exacerbation of renal insufficiency suitable for an attempt to tide over the condition for the few days needed for resumption of better renal function To such forms of uremia peritoneal irrigation offers a probably effective therapy

If these measures are ineffective and renal insufficiency continues and progresses, soon the patient is in the phase of definite uremia and treatment unfortunately is only partially effective In such patients the problem that is presented is to reduce azotemia as far as is possible, to correct acidosis and to maintain hydration and nutrition Of course the ideal treatment would be in measures to increase elimination of retained toxic substances by kidney or other routes. Bleeding is one means of elimination, but it is inadvisable if anemia is marked even if the blood withdrawn is replaced by transfusion of normal blood Bleeding however may help temporarily and can be tried if followed by replacement transfusions In past years vigorous catharsis colonic irrigations and sweating were used as means of vicarious excretion of toxic products Some elimination was accomplished but it was slight and the procedures were debilitating and upsetting far byond any beneficial results Consequently these methods have been abandoned very generally No longer do I advise them Theoretically diuretic drugs should increase renal elimination Actually they usually decrease urine output, when renal function is defective and may act as renal irritants so their use is not advised for the management of uremia

If there is no nausea or vomiting patients with uremia should receive the low protein diet already mentioned *fluid intake should be increased up to 3 000 to 5 000 c c* unless edema or signs of cardiac decompensation appear if either is in evidence fluid intake should be reduced It is well to give part of this fluid intravenously and slowly in the form of 1 000 or 500 c c of 5 or 10 per cent. solution of glucose daily for several days Many of these patients with such increase in fluid intake need supplemental sodium chloride as indicated by determination of blood chloride, and this can be given daily in addition to that in the diet as 1 to 3 enteric

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encephalopathy as a cause lumbar puncture may bring relief and is worthy of trial In some patients sedation with bromides or barbiturates suffices for control of the restlessness In many however more powerful sedatives such as chloral hydrate and paraldehyde are required and these may have to be given in large doses by rectum or intravenously, since so often these patients vomit the drug if mouth dosage is attempted The following doses have been recommended chloral hydrate gm 2 to 4 (gr 30 to 60) in olive oil by rectum or paraldehyde 10 to 30 c c ($\frac{1}{2}$ to $7\frac{1}{2}$ drams) in olive oil by rectum paraldehyde may be given also slowly intravenously in doses of 4 to 7 c c diluted with several hundred volumes of normal salt solution many however regard this procedure as dangerous and prefer rectal dosage in all patients except those with an irritated rectum preventing retention of the drug given by that route Morphine sulfate subcutaneously in doses of 15 mgm ($\frac{1}{4}$ grain) repeated if necessary in some patients works better than anything else Morphine is not contraindicated by the depressed kidney function in these patients as many physicians believe at least that has been my experience, however as excretion is slowed large doses are contraindicated In some patients warm baths have a calming influence but they should not be so prolonged or so hot as to debilitate these patients further When used the patient afterwards should be wrapped in a blanket

Muscle Twitchings — In numerous patients oft repeated or almost continuous localized or widely distributed muscle twitchings are prominent and very disturbing features These more frequently are uremic than encephalopathic in origin They are to be distinguished from tetany which develops in some of the patients with chronic non-edematous Bright s disease as described in another section *For them sedation may be used as described in the previous paragraph* on Psychic and Motor Restlessness Another therapeutic approach is the utilization of intravenous doses of calcium chloride or calcium gluconate 10 to 15 c c of a 10 per cent solution of the former or 15 to 30 c c of a similar solution of the latter Unfortunately the effect of calcium is not long lasting and repetition is necessary which detracts from its usefulness in this situation In patients with only slight anemia bleeding can be carried out and the removal of 200 to 300 c c of blood may have a striking effect in some of these patients Unfortunately developing anemia limits this form of treatment very greatly

Convulsions — They are of encephalopathic origin more often than of uremic Lumbar puncture is advisable Sedation as already described in the two preceding paragraphs *is advisable in the hope of preventing them or lessening their* severity Bleeding in non anemic patients is advisable as for muscle twitchings When convulsions occur and are severe they are controlled best by chloroform inhalations the chloroform given by the drop method on a mask so called *open* method the amount used and duration of the inhalation of chloroform should be just enough to control the convulsive seizure

coated tablets of 1 gm each If there is obtained evidence of acidosis by appropriate tests, 3 to 6 gm of sodium bicarbonate should be given daily by mouth If nausea and vomiting exist, we must rely largely on intravenous glucose, amino nitrogens plasma blood or albumin for nutrition, in the hope that nausea and vomiting will abate to allow of return to partial or complete feeding by mouth For this purpose 3 000 c c of 10 per cent glucose solution and 1 000 c c of 85 per cent sodium chloride solution should be given intravenously each 24 hours by continuous drip or repeated slow injections Glucose for optimum utilization should not be given faster than 1 gram per kilogram of body weight per hour In addition to glucose and saline solutions these patients should receive daily intravenously 25 grams of purified human albumin, if this is available If this form of albumin is not available amino nitrogen preparations, plasma or whole blood may be used, remembering that approximately 500 c c of these can be considered the equivalent of 25 grams of the purified human albumin The whole blood would have an advantage in the presence of anemia Addis and his associates[458] have pointed out that decreased renal function with serious consequences may follow such injections, if they are pushed byond certain limits to be determined by observing their effect on renal function as measured by available tests of renal function in general use

With vomiting usually there is loss of much chloride and a greater degree of acidosis These conditions should be determined by appropriate quantitations, and when present these patients should receive sodium bicarbonate or other alkali and added sodium chloride as described in the previous paragraph

The methods just described are the best measures available to combat nausea and vomiting in the uremic patient Sometimes gastric lavage with warm, normal saline solution by stomach tube will decrease nausea and vomiting Drugs and many have been tried usually do very little to decrease severe nausea and vomiting Cocaine by mouth in 15 mgm (¼ gr) doses is said to diminish vomiting however and may be tried Not infrequently drugs given for these symptoms seem to increase the nausea and vomiting and it is best to omit them

In these various phases of uremia, as high blood pressure and vascular lesions are the rule care must be taken against precipitating cardiac decompensation with possible pulmonary edema by introducing excess fluid into the body Fluid should be given slowly and digitalis therapy utilized, along with oxygen therapy, as in other forms of cardiac decompensation, whenever there is evidence of circulatory deficiency

Psychic and Motor Restlessness — Restlessness both psychic and motor, frequently is a disturbing factor to patients in the later stages of chronic non-edematous Bright's disease Such restlessness may be caused by both uremia and encephalopathy, often both causes are in action Sometimes acidosis is a factor in the cause, and improvement results when it is corrected by alkali therapy With

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Tetany — This is infrequent in chronic Bright's disease, but it may occur either from hyperventilation, from persisting vomiting or from alkalosis The former type may be from the forced breathing of acidosis and, if so, can be controlled by correcting the acidosis When due to vomiting, measures to control vomiting should be used, although it is to be recognized that often they fail If alkalosis is of therapeutic origin, giving alkali should be stopped at once The manifestations of tetany can be controlled by giving calcium as outlined under Muscle Twitchings The tetany is to be recognized by the usual signs, in particular the presence of positive Trousseau's and Chvostek's signs

Headache — This is a frequent and often a very disturbing symptom difficult of control Such drugs as acetylsalicylic acid, acetphenetidin, amidopyrin, caffein phenobarbital, etc should be tried Codein may be needed, that failing, morphine can be used, but is should be avoided as long as possible, if probable duration of life makes avoidance of habituation a consideration In numerous patients headache is related to increased intracranial pressure In these patients edema of the optic disc is an important sign of such increased pressure Methods to reduce intracranial pressure are indicated, when it is present, such as the injection of hypertonic solutions intravenously Fifty per cent glucose or sucrose 100 c c can be used the latter has a more prolonged effect the injections can be repeated once or twice daily In many patients lumbar puncture with manually slowed flow of intraspinal fluid is effective There is danger, however, in this from the edematous brain crowding the pons and medulla down into the foramen magnum and by pressure stopping the function of the respiratory center, causing immediate death Consequently when ophthalmoscopic examination shows a considerably swollen optic disc, lumbar puncture should not be carried out until pressure has been reduced by hypertonic solutions

Blackfan and his associates have recommended the use of magnesium sulfate intravenously for vomiting, headache and convulsions in patients with Bright s disease to children they gave slowly by vein 10 c c per kilo of body weight of a 2 per cent solution of magnesium sulfate Fishberg for adults recommends a dose of 20 c c of a 10 per cent solution given similarly These injections may be repeated at 2 hour intervals if necessary Should respiratory depression result from the magnesium a 5 per cent solution of calcium chloride given intravenously will be an antidote to this

Pruritus — This is another of the marked discomforts that plague the patient with advance non edematous Bright s disease and like the other discomforts is difficult to ameliorate In its milder form relief may be obtained from warm alkaline or bran baths or from sponging the skin with a weak solution of sodium bicarbonate or phenol (1 per cent) or from the application of a 5 per cent menthol ointment, white wash" i e calamine lotion, or a mixture of equal parts of benzyl alcohol ethyl alcohol and water the taking of glyceryl trinitrate or eryth

rityl tetranitrate or of small doses of pilocarpine etc These failing the following procedures have been recommended histamine (0 25 mgm) hypodermically twice a day, ergotamine tartrate 1 mgm (gr 1/60) by mouth 3 times a day sodium bromide intravenously with the latter on account of defective renal excretion toxic phenomena are so likely to occur that the use of this drug scarcely seems advisable Unfortunately often none of these remedies are effective and nothing is left to do but to attempt to apply sufficient sedation to lessen the patient s sensation of the itching The multiplicity of remedies suggested for pruritus including the numerous ones just enumerated is suggestive that a satisfactory form of treatment still is lacking

CERTAIN SPECIAL SYNDROMFS OF BRIGHT'S DISEASE

Kimmelstiel Wilson Syndrome

This term is given to a symptom complex[140] which develops most often in patients with diabetes mellitus but occasionally in patients who do not have diabetes mellitus[140 141 377 378 396 404–406] Its features are hypertension, marked albuminuria generalized edema lowered plasma protein and sometimes, lowered basal metabolism Often as it progresses renal function decreases as indicated by lowered phthalein excretion and elevated non protein blood nitrogen Later in its course typical uremic manifestations may appear with increasing azotemia Its clinical and laboratory features are those already described for the edematous type of Bright's disease or the nephrosis syndrome with the added features, hyper tension, decreased renal function with increasing azotemia, diabetic glucosuria and various complications incident to diabetes mellitus As hypertension is usual, to all of these may be added any of the circulatory features of high blood pressure and cardiovascular lesions

As already described in Part I, the kidney from these patients almost always shows the pathological lesion intercapillary glomerulosclerosis, but the lesion may be found also in patients who have not shown the Kimmelstiel Wilson syn drome during life, although usually they have had diabetes mellitus It has been stated that the Kimmelstiel Wilson syndrome i e the nephrotic syndrome, occurs in only 6 3 per cent of diabetic patients with intercapillary glomerulosclerosis, i e if included are kidneys with the lesion present but not extensive or gener alized

The Kimmelstiel Wilson syndrome usually appears in patients past 50, al though cases have been reported at earlier ages but very few under 40

If a diabetic patient develops well marked albuminuria the Kimmelstiel Wilson syndrome is likely to develop If there is hypertension this likelihood is increased If with hypertension cardiac hypertrophy ensues cardiac decompen sation with edema of circulatory origin is a probability and this edema must be distinguished from that of renal origin With the latter albuminuria almost always is marked and persistent with the former albuminuria may be marked but will decrease if cardiac decompensation is controlled by digitalis therapy In some patients both varieties of edema may be present at the same time this renders the recognition of the presence of the Kimmelstiel Wilson syndrome diffi cult careful consideration of the development of symptoms and signs and re peated examinations of the urine however should make possible its recognition

Treatment of the Kimmelstiel Wilson syndrome is not apt to be very successful

Treatment of the nephrosis syndrome should follow along the line described under Treatment in the preceding discussion of Acute Subacute and Chronic Edematous Bright s Disease (Nephrotic Syndrome of Bright s Disease) unless the presence of diabetes mellitus and hypertension has introduced features antagonistic to this *Mercurial diuretics as described there should have a thorough trial* if edema of renal type is generalized Obviously the diabetes mellitus must be controlled continuously by adequate insulin in relation to carbohydrate in an optimum diet Any signs of cardiac decompensation will need in addition to diuretics adequate dosage of digitalis Any other features related to the patient s hypertension should have therapeutic management as discussed elsewhere in Oxford Medicine

If azotemia develops as often it does the protein content of the diet which probably has been increased in view of the nephrotic syndrome must be curtailed sharply and fluid intake increased as much as the cardiocirculatory situation will allow realizing that increased fluid intake may increase the edema of renal origin As in any severe diabetic diabetic coma is a possible serious complication to be guarded against and treated promptly if it develops as described in the chapter on Diabetes Mellitus With the foregoing complexities *prognosis* for the Kimmelstiel Wilson syndrome obviously is poor even with the most skilled therapeutic management

Bilateral Cortical Necrosis of the Kidney

The pathology and probable causes of bilateral cortical necrosis of the kidney[382–3 6 389 390 396 407 408] has been described already in the section Pathology in Part I Whatever *the antecedent disease* the clinical picture of cortical necrosis of the kidney is always in its essentials the same Rapidly oliguria appears quickly followed by anuria In many patients anuria is immediate and persistent If any urine is obtained for examination moderate to no albuminuria casts leucocytes red cells and possible gross hematuria will be demonstrated

Usually there i pain and tenderness in the loins or in the epigastrium extending later into the loins With the anuria the blood shows a rapid increase in tho e constituents normally excreted by the kidney notably non protein nitrogen urea and creatinine Disturbance of vision are unusual Ophthalmoscopic examination often shows edema of the discs sometimes hemorrhagic or white areas Blood pressure increase is unusual Edema of dependent parts may occur Slight fever is frequent occasionally temperature goes to 105° or 106° *F* *Leucocytosis* 10 000 to 40 000 often is found Mental clarity is maintained *remarkably* but drowsiness to coma comes later in the course of disease with terminal twitchings of muscles or frank convulsions to be expected

In 71 cases 52 died within 4 to 12 days[382] but some live much longer one case

living 32 days[407] A few cases probably recover[408], because necrosis is not very extensive, but diagnosis in these cases is very problematic Obviously, when such wide spread cessation of circulation in the renal cortex develops as in these patients, no therapy can be expected to be of help If less widespread a lesion forms intravenous glucose solution with bleeding followed by transfusion of compatible blood might tide over an acute situation until slightly damaged portions of the kidney regain function The[409] method of peritoneal irrigation[436 437], described elsewhere in the discussion of treatment of uremia, would give the greatest chance of such recovery

Bilateral Papillary Necrosis

Necrosis of the renal papillae, sometimes termed papillitis necroticans or necrotizing pyelonephritis, is another lesion in pathogenesis somewhat related to bilateral cortical necrosis of the kidney, i e it results from a blocking of the blood supply of the papillae in this instance however, the blocking caused by an inflammatory process which appears to begin as a small abscess in the papilla and then extends to stop the nutritive blood supply[481] This is an infrequent lesion found most often, 19 of 26 cases[481] and 29 of 859 diabetics in a series of 32,000 necropsies[490] in diabetic patients with latent or subacute pyelonephritis It is more common in women and is rare under 40 years of age[490] It may occur also in non diabetic patients, in 21 of 1 023 patients with pyelonephritis but without diabetes[490] usually those with urinary obstruction as from prostatic hypertrophy In such patients suddenly there are evidences of severe, systemic infection, with pus in the urine, associated aliguria and rapidly rising non protein or urea nitrogen

A retrograde pyelogram, if the patient s condition allows, might show a filling defect due to necrosis and sloughing of the papilla The bacteria in such patients have been *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae* or *Streptococcus hemolyticus* or *viridans*

Rarely unilateral the kidney shows small abscesses in the pyramids at a level about two-thirds the way from the tip of the papilla to the juncture of cortex and papilla, later becoming confluent to cause complete necrosis of the terminal two-thirds of the papilla and appearing as areas of yellow brown or yellowish green necrosis sharply demarcated by a narrow zone of paler, yellow to green tissue with a peripheral zone of reddish congestion, an appearance like other infarcts of the kidney

If the lesion is suspected chemotherapy with penicillin and treatment of the azotemia with increased fluid by mouth and parenterally is indicated Peritoneal irrigation might be effective Nephrectomy cured two cases, presumably having unilateral lesions

Traumatic Uremia Crush Syndrome Myoglobinuria

The above terms have been used for a renal insufficiency syndrome that develops following severe traumata especially crushing injuries[388,391-393,396] The majority of these patients suffer from severe shock from which they recover under treatment appropriate to the condition of shock but in from 4 to 17 days later oliguria progressing to anuria may appear to be recovered from or to continue to death of the individual The pathological changes in the kidney have been described in Part I

In shock itself with low blood pressure and decreased blood flow urine excretion decreases or for a time stops and a proportionate azotemia results With therapeutic reversal of the shock syndrome in most patients renal function is restored but in some this does not happen, and the renal insufficiency syndrome here under discussion has developed

In other individuals as already mentioned the syndrome develops later to be serious or even fatal after apparent recovery from the primary shock In these patients the syndrome is fatal after a few to 8 or 9 days sometimes after a longer period with azotemia and the symptoms described already under Bilateral Cortical Necrosis of the Kidney

The cause of this syndrome seems to be primarily toxic toxic substances being formed in the crushed tissues of the body or from bacteria growing in them Muscle crushing often is prominent in these patients and muscle pigment myoglobin, is set free taken up in the circulation and excreted by or deposited in the kidney It may follow arterial occlusion also, possibly initiated by reflex vascular spasm[467]

Myoglobinuria occurs also in Haff's disease a toxic condition caused by eating certain poisoned fish This heme pigment may be a further or according to some the chief causative toxic factor Some believe that the pigment deposits in the kidney only obstruct the excretion of urine others consider that the myoglobin has only a slightly injurious effect A positive benzedine test in the urine and pigment containing casts are suggestive of myoglobinuria. Myoglobin can be recognized spectroscopically The action of methemoglobin once thought to be important now is believed to be uninjurious[394] Acidosis may play some causative part, usually it is present Alkalinization early of the urine may prevent or greatly decrease renal insufficiency

In 6 cases Goormaghtigh[497] found evidence that renal deficiency in these patients is to a great extent the result of vasoconstriction followed by paralytic vasodilatation involving first the post glomerular arterioles and later the glomerular tufts He accounts for the gradual increase in blood pressure in these cases by increase in the afibrillar cells of the media of the preglomerular arterioles which acquire cytological features of glandular activity

Another view as to the cause of this syndrome is that the kidney swells, and the tense tissue retards renal circulation It is said that the kidneys from these patients are found to be swollen with tense capsule, and when incised and sectioned, the kidney everts[10] On the basis of these observations bilateral incision and stripping of the kidney capsule is advised as soon as oliguria becomes marked, and a large fluid intake is considered to be inadvisable Those not holding this view advise giving isotonic (1 75 per cent) sodium lactate solution along with physiological salt solution or 5 per cent glucose solution, beginning as soon as oliguria develops

HEMOGLOBINURIA BLACKWATER FEVER TRANSFUSION RENAL REACTION

Whatever its cause and they are various, red blood cells hemolyze and hemoglobin is set free From it methemoglobin or metalbumin form These with acid hematin are excreted and deposited in the kidney The urine becomes burgundy red or brownish red, so called porter or stout color to continue the simile of beverages Albuminuria and cylindruria with heme pigment granules in the casts appear the casts usually show granules of heme pigment Oliguria, often progressing to anuria develops with consequent azotemia Acido is is present and the urine is highly acid so that therapeutic alkalinization is difficult There is fever often with chill The kidney shows the changes described in the immediately preceding section with the addition of heme pigment granules in tubular epithelium and in casts

Various explanations of the renal insufficiency in these patients have been given The one at first generally believed in was tubular obstruction by the precipitated heme pigment and casts, but the expected dilatation of tubules was lacking or at least not prominent, and so this explanation has been abandoned by most observers

The following explanations now have supporters (1) toxic degeneration of tubular epithelium (2) circulatory deficiency either from obstruction of arterial branches or from low blood pressure, (3) edema causing swelling of the kidney to increase intrarenal pressure to the point of hindering circulation and interfering with the formation and outflow of urine Although renal cell changes indicate the action of some toxic substance hemoglobin in itself seems non toxic, and so the presence of some other heme pigment derived from hemoglobin or some toxic body unrelated to hemoglobin must be predicated to support the toxic theory of the cause of the observed renal changes

The *treatment* generally recommended is to give alkali to neutralize the acid urine and to increase fluid intake by mouth or parenterally One group advocate early bilateral renal decapsulation without increasing fluid intake, claiming best results from this procedure when urine excretion has been greatly decreased

Sulfonamide Kidney

The sulfonamide kidney[412–416] shows several forms of injury The widespread therapeutic use of drugs of the sulfonamide group has made important the early recognition of consequent renal damage[416–417] and more important its prevention The latter does not concern us in this chapter however maintaining an alkaline reaction to the urine during dosage with sulfonamides almost always suffices for prevention of sulfonamide injury to the kidney

The most frequent form of renal injury is caused by the deposition in the *tubules and to a less extent the glomeruli of crystals derived from the sulfonamide* in therapeutic use These patients show crystals and red cells in the urine and often moderate oliguria More serious but fortunately less frequent is the more marked oliguria or anuria caused by crystal deposits and concretions derived from them in collecting tubules kidney pelvis or ureters In the excreted urine usually there are crystals and red cells but both may be lacking

Still more serious but more infrequent is the form of sulfonamide kidney that results from degeneration to necrosis of tubular epithelium degenerative and infrequently proliferative lesions of the glomeruli and edema of the interstitial tissue There may be also crystal deposition in these kidneys Marked oliguria followed by anuria develops quickly in these patients and azotemia develops and progressively increases In such urine as is secreted albumin red cells and casts are the rule Sometimes crystals are found Sometimes these patients develop subcutaneous edema

The patients with only microscopic or macroscopic hematuria as a rule clear promptly with cessation of the sulfonamide giving sodium bicarbonate by mouth to the point of making the urine alkaline and markedly increasing fluid intake *This is true too if moderate oliguria exists before increasing fluid intake If* oliguria becomes marked or if anuria develops the outlook is not so good The previous treatment should be extended in these patients to include intravenous isotonic (1 /5 per cent) sodium lactate solution and free ureteral and pelvic irrigation with warm 10 per cent sodium bicarbonate solution

If these methods do not speedily start satisfactory urine excretion the very serious toxic degeneration of the kidney is probable In this group sodium lactate solution by mouth and intraperitoneally i indicated and many advise prompt bilateral decapsulation of the kidney with irrigation of kidney pelvis and ureters with warm 10 per cent sodium bicarbonate solution

In all of the patients with anuria caused by sulfonamides mortality has been high Prompt institution of the suggested treatment is imperative if life is to be saved Very general recognition of the potential danger to the kidneys of the sulfonamides and of the importance of prophylactic alkalinization of the urine with commencement of sulfonamide dosage has reduced serious renal lesions to a

number very small in proportion to the enormous number of patients who have been receiving sulfonamides

Hepatorenal Syndrome

The lesions and the probable etiology and mechanism of the hepatorenal syndrome[417–421] already has been discussed in the section on Pathology in Part I Usually evidences of disturbance of renal and of hepatic function appear simultaneously but sometimes hepatic dysfunction is in evidence before renal insufficiency becomes evident Jaundice is present in many of these patients Albuminuria appears with oliguria and in more serious cases, anuria with azotemia, this appearing from a few days to 2 weeks after operation Some have periodic hematuria[417] some have hypertension[417] Often these patients die *Treatment* should be as discussed in the three preceding sections

Amyloidosis

In the present period renal amyloidosis[397 398] is rare except in patients with pulmonary tuberculosis and in these patients it appears to be decreasing so far as the forms with sufficient extent of involvement to cause symptoms is concerned It does occur in patients with long continued bacterial infection such as osteomyelitis bronchiectasis and empyema thoracis, but such cases of renal amyloidosis are decreasing in frequency steadily Syphilis and neoplasms, notably multiple myeloma, are occasional causes Rarely amyloidosis of the kidney is idiopathic in the sense that there is no accompanying disease to explain its development[397] Usually amyloidosis is present elsewhere in the body, most often in both liver and spleen but isolated amyloidosis of the kidney may occur, or amyloidosis elsewhere may be of very slight degree The pathology of renal amyloidosis has been described already under Pathology in Part I

Patients with idiopathic amyloidosis are important in clinical medicine, since they present the symptomatology and signs of amyloidosis uncomplicated by an other serious disease condition Furthermore as at times amyloidosis is slight except in the kidney or is chiefly in the spleen in addition to its presence in the kidney, where it produces few or no symptoms or only those caused by the increased size of the spleen these patients give satisfactory evidence of the deleterious influence of renal amyloidosis on renal function For these reasons patients with idiopathic amyloidosis have been selected as illustrative cases

Case XXVII — A man 51 years old was admitted to the hospital P B B H Med No 28 944 on December 10 1926 and subsequently on October 18 1927, December 12 1927 and May 24 1928 He died on May 25 1928

This patient was a plumber but had no contacts with lead in the sense of ever hav

ing anything to suggest lead poisoning At the age of 25 he had pneumonia and at the age of 25 and again at 43 he had gonorrhea otherwise his health had always been good Fifteen months prior to his admission to the Peter Bent Brigham Hospital in November 1926 he had noticed the beginning of swelling of his legs and ankles which began insidiously and did not produce any great inconvenience and practically no symptoms for a long time Three or four months after this began he had a number of badly infected teeth removed but this had no effect on his condition

When he came to the hospital *physical examination* showed nothing but generalized subcutaneous edema with a slight amount of free fluid in the abdominal cavity His urine showed a large amount of albumin with a good many hyaline and granular casts a moderate number of leucocytes and no red blood cells His blood pressure was 145/80 His Wassermann reaction was negative At this time the figures for his phthalein excretion ranged from 33 to 45 per cent his blood urea nitrogen from 13 to 25 mgm per 100 c c and his blood cholesterol from 213 to 217 mgm per 100 c c His basal metabolism was as low as −25 but this was increased by thyroid in large doses which incidentally had no effect on his edema

After going home his edema continued about the same and there was no change in the characteristics of his urine or in the phthalein excretion and blood urea nitrogen levels His plasma protein varied between 5 2 and 5 7 with albumin 2 7 and globulin 2 5 and albumin 3 6 and globulin 2 respectively Gradually the edema increased At times there was a large diuresis from salyrgan and some decrease in the edema as a result

An *autopsy* gave the following diagnoses amyloid and lipoid nephrosis generalized edema hydroperitoneum hydrothorax amyloidosis of kidneys spleen liver and adrenals terminal pneumonia

Kidneys —The right kidney weighed 295 grams the left 300 Capsules stripped easily from a smooth surface the kidneys seemed rather soft larger in size than usual and edematous Cut surface showed a diffuse yellowish somewhat granular appearance without any signs of scarring Microscopic examination showed the kidney substance to be edematous the tubules in many instances dilated with a considerable degree of degeneration of the tubular epithelium even though the postmortem examination was done one hour after death The most important lesion was a marked deposit of amyloid along the capillaries of the glomerular tufts fatty degeneration in the glomerular epithelium amyloid in other vessels of the kidney and extensive amyloid deposit also in the spleen liver and adrenals The amyloidosis seemed to be entirely idiopathic in the sense that none of the usual causes of amyloid were present at autopsy or suggested by the patient s clinical history

Summary of Case XXVII —A man of 51 had extensive edema for about four years with a urine continuously showing large amounts of albumin a moderate number of casts no red cells no marked reduction in phthalein excretion and no great increase at any time in blood urea nitrogen no hypertension Death came from a terminal infection This edematous form of Bright s disease was caused by amyloidosis which in itself must be called idiopathic In this patient the amyloidosis of the glomeruli caused marked albuminuria without renal in

sufficiency of the retention type In other words it produced the nephrotic syndrome There was neither hypertension nor azotemia

Case XXVIII — A man aged 64 admitted to the hospital on May 28, 1932, P B B H Med No 41 159 with subsequent admissions on July 30, 1932, Med No 41 500 and on November 7 1932 Med No 41 992 The patient died November 12 1932 The patient had had typhoid fever in 1889 and seven years later apparently another attack There was no history of other infectious diseases He seems to have been quite well and active until March 1932 when he was admitted to the medical service with blood pressure 215 mm Hg, systolic 95 diastolic, a red blood count of 2 390 000 a hemoglobin of 60 per cent a large trace of albumin in his urine with many casts At this time his phthalein excretion was 10 per cent and a little later his blood urea nitrogen was 67 mgm per 100 c c

About four weeks before his medical admission in May 1932 he began to note dyspnea on exertion gradually increasing and he also noticed that he was getting very weak and that he began to have some edema of his ankles with nocturia one or two times at night

Physical examination — Ophthalmoscopic examination now showed some narrowing and tortuosity and distinct nicking at the arterial venous crossings but no hemorrhages or exudate The heart was moderately enlarged His blood pressure rose in the hospital to 20/900 on June 2 210/95 on June 16 240/100 on June 23

Blood urea nitrogen ranged during this admission between 54 and 82 mgm per 100 c c and his phthalein excretion from 5 to 8 per cent His urine had a fixed specific gravity of 1 010 or less with a slight trace of albumin The sediment showed an occasional red cell and white cell and a few hyaline or granular casts

Prior to this last admission the patient became irrational disoriented unresponsive to questions His respiration was slow he seemed pale skin showed many scratch marks Ophthalmoscopic examination showed extensive vascular changes and several small hemorrhages and some exudate along the vessels His heart was moderately enlarged with a loud systolic murmur His blood pressure was 210/110 His urine showed a large trace of albumin with the same sediment as previously His hemoglobin was now 65 per cent red cell count 2 540 000, white cell count 8,900 Patient rapidly went down hill and died on November 12

Autopsy — Diagnoses chronic glomerulonephritis renal amyloidosis extensive amyloid infiltration of the vessels of the kidneys, adrenals lung liver spleen pancreas thyroid prostate myocarditis chronic fibrinous bronchopneumonia slight pleural effusion bilateral pericarditis fibrous pericarditic effusion slight, ascites, slight, tuberculosis healed apical pulmonary

The fibrinous pericarditis was very slight and limited to the right auricle The heart weighed 360 grams The valves seemed normal The myocardium seemed slightly pale but showed no gross lesion

Kidneys — The right kidney weighed 80 the left 65 grams was of normal shape surrounded by a considerable amount of fairly adherent perirenal fat Capsules were generally thickened and on stripping were found to be quite adherent to the surface of the kidneys although they can be stripped away without tearing the surface Kidney surfaces were rough, granular mottled with yellowish pink areas in which there were a

few small round cysts The kidneys cut with considerable resistance and the knife seemed to grate slightly in the papillary region The cortex was irregularly contracted varying from 1 to 4 mm in width Cut surface was pale yellowish brown *The cortex* was but poorly differentiated from the medulla Calices and pelves were not abnormal in shape and were not dilated Kidney sections showed extensive amyloid infiltration both interstitial and vascular and extensive glomerulonephritis There was a tremendous increase in the interstitial tissue largely of homogeneous palely staining hyaline like character With this there was very little cellular infiltration The glomeruli were extremely distorted and were converted into masses of hyaline like material which was *structurally palely staining homogeneous resembling that found in the* interstitial tissue This substance was extracellular and had spread the few remaining cells of the glomeruli apart so that they formed merely occasional single layered boundaries about it In most of the glomeruli the capsular spaces had been entirely obliterated because of fusion between the hyalinized tufts and the thickened capsules In a few irregular remnants of the tuft capillaries could be found The tubules in general although less severely effected than the glomeruli were somewhat collapsed their cells *undergoing necrotic changes Those which remained were slightly dilated lined by* thin small and flattened epithelium in which many refractile hyaline bodies could be seen The vessels of the kidney from the larger arteria recti to the small glomerular afferent vessels showed an extreme degree of intimal hyperplasia and medial hyalinization which in many had resulted in almost complete occlusion of their lumina Those intertubular capillaries which remained were congested and filled with red blood cells Special stains for amyloid showed the greater amount of the hyaline like material mentioned *above to give the amyloid reaction This was most marked in the glomeruli* although considerable interstitial areas stained similarly

Summary of Case XXIII — This patient clinically was a case of chronic non-edematous Bright s disease with hypertension and renal insufficiency present when symptoms first appeared Thereafter his course was brief he died in about 6 months His kidneys were very small The kidneys seemed to show amyloidosis as a very important factor in the pathogenesis of the chronic renal lesion There was no histological evidence of an antecedent glomerular lesion such as is found in acute and subacute glomerulonephritis but as time went on amyloid deposits in the glomeruli hindered glomerular filtration and brought about renal insufficiency of the retention type with azotemia and in the earlier stages of the disease slight albuminuria This patient had hypertension

A presumptive diagnosis of renal amyloidosis is justified when in any of the conditions in which amyloidosis may develop especially in patients with long continued pulmonary tuberculosis albuminuria and cylindruria appear and continue The presence of renal amyloidosis is more probable if spleen and liver are enlarged

A positive diagnosis can be made by means of the Congo red test The more rapidly and more completely the Congo red disappears from the circulation the

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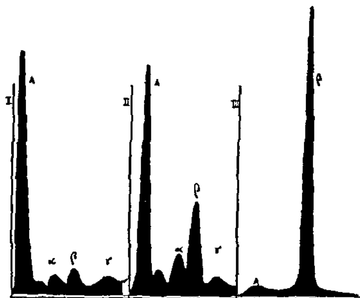


FIG 40 Electrophoretic patterns (ascending limbs) of I normal human blood serum II serum of patient with multiple myeloma and III urine of same patient from Blackman and Associates [426]

SARCOIDOSIS OF KIDNEY[455 456 457]

Sarcoidosis is a generalized granulomatous disease of unknown etiology which may involve any part of the body Involvement of multiple tissues is the rule Sarcoid may involve the kidney this involvement is less frequent than of many other tissues Renal involvement may be devoid of any evidence that the kidney is involved many of the reported cases have shown no symptoms pointing to renal involvement (3 of Longcope s[456] 4 cases) Rarely (4 reported cases) there are renal symptoms albuminuria fixation of specific gravity increased blood urea and non protein nitrogen and decreased phenolsulfonephthalein excretion

Hyperglobulinemia hypercalcemia and anemia have been observed as in renal insufficiency from multiple myeloma Very interesting are retinal changes in some of these patients changes which appear not to be caused by the renal insufficiency but to be a local change in the retina due to the sarcoidosis as they have been observed in patients without lesions in the kidney In the retina the vascular lesions involve the veins which are constricted and irregular in caliber some thrombosed others replaced by fibrous bands Numerous deep and superficial flame shaped hemorrhages a few vitreous hemorrhages and macular stars have been seen The discs my be hazy Sarcoid granulomata may appear in

more probable the presence in the body of amyloid A positive test, however, obviously can occur when the amyloid deposits are elsewhere in the body than in the kidneys There is nothing pathognomonic of renal amyloidosis in the character of the excreted protein or the appearance and composition of the casts It is doubtful whether casts with any frequency contain amyloid, anyhow not often enough to justify applying stains for amyloid to urinary sediments for the purpose of diagnosis

Clinically besides the urinary findings already noted amyloidosis presents the symptoms signs and progression most frequently of chronic non-edematous Bright s disease as already described under that heading (Case XXVIII) Much less frequent is the clinical development of the edematous form of Bright's disease or nephrosis syndrome (Case XXVII) In these clinical developments there is nothing in themselves to point to renal amyloidosis as their cause In some patients it seems quite certain that amyloid deposition has taken place in a kidney already having developed the pathological lesions of Bright's disease

Treatment should be as described for the particular type of Bright's disease clinically simulated by the kidney with amyloidosis Beyond treating the underlying factors in the patient apparently causative of the amyloidosis, there is no specific therapy for amyloidosis *Prognosis* in these patients is poor, but amyloidosis should be considered only a contributory factor in it

Myeloma Kidney

In multiple myeloma[4 3–4 7] Bence Jones protein, a beta globulin, is present in considerable amount in the blood plasma and is excreted in the urine Plasma protein may be increased above normal values and differentiation shows the presence of the beta globulin fraction in increased amount (Fig 40) Sometimes this increase is great sometimes slight The protein in the urine usually is large in amount and gives the usual tests for Bence Jones protein, namely precipitation on heating with subsequent clearing as the urine is brought to the point of boiling There is no fixed parallelism between the amounts of Bence Jones protein in plasma and urine Rarely it appears in crystalline form Electrophoretic studies (Fig 40) show increase in beta globulin in blood serum and that it is the chief constituent of the protein in the urine, with it often there is present in the urine a slight amount of albumin The symptoms of renal origin in these patients, if they occur, are like those of chronic non edematous Bright s disease, usually with azotemia Many patients with multiple myeloma continue to have normal or nearly normal renal function Oliguria to anuria with proportionate multiple myeloma is a progressive disease, fatal in varying lengths of time In some renal insufficiency with azotemia dominates the late stages of this progression

functioning kidney inadvertently had been removed for a long time they remain with clear mentality and only terminally if at all develop uremic muscle twitchings or convulsions In an occasional patient only a progressive anemia is in evidence its real cause not recognized until enlarged kidneys are felt in each flank and/or low or zero 'phthalein excretion and/or high total non protein or urea nitrogen are discovered If only one kidney is palpable as sometimes happens these patients sometimes are considered mistakenly to have malignant neoplasms causing anemia possibly nausea and vomiting the latter actually due to renal insufficiency

Case XXIX — A young woman of 44 was admitted to the hospital on November 22 1930 July 25 1934 and June 6 1935 dying on June 18 1935 P B B H Med Nos 38,015 45 251 and 46 997 This patient first entered the hospital in November 1930 on the surgical side complaining of generalized body aches and tenderness over the right flank At this time a tender mass was palpated in the right upper quadrant which was thought to be a kidney or mass attached to it The urine was grossly cloudy Cystoscopic examination showed normal appearing ureteral orifices with clear urine on the left and cloudy urine on the right Pyelograms of both kidneys showed irregularly dilated pelves having the appearance of polycystic kidney A 7 foot film of the heart showed it to be just inside the upper limits of normal At this time the urine showed numerous white cells rare red cells no casts and had a specific gravity of 1 020 without albumin The blood urea nitrogen was 11 mgm per 100 c c Red blood cells were 3 650 000 white blood cells 11 750 hemoglobin 70 per cent During this stay the patient for a few days had fever from 100 to 102 F after that normal temperature

At home she continued to have varying fever and not infrequently sweated at night but in the hospital she did not have any fever *B coli* was cultured a number of times from her urine In May 1933 her phthalein excretion was 10 per cent her blood urea nitrogen 32 mgm per 100 c c Her blood pressure then was 170 mm Hg systolic 100 diastolic A year later her blood urea nitrogen was 60 mgm per 100 c c her phthalein excretion had dropped to 2 5 per cent Her blood pressure was 180 systolic mm Hg 95 diastolic She had had increased nervousness and palpitation and shortness of breath with nocturia once nightly She had lost twenty pounds in two years

Now in June 1935 she looked pale her red cell count however was 3 040 000 white cell count 5 750 hemoglobin 62 per cent A mass about the size of an orange could be felt in the region of the right kidney and a small one in the region of the left kidney Ophthalmoscopic examination showed no abnormality except a very slight thickening of the blood vessels Specific gravity of the urine was fixed at 1 010 in it there was a very light trace to slightest possible trace of albumin many white cells and very rarely a brown granular cast Blood urea nitrogen now varied between 82 and 106 mgm per 900 c.c Phthalein excretion soon became 0

After leaving the hospital on September 2 1934 she continued to come to the O D D Her blood pressure remained at about 170 mm Hg systolic 105 diastolic Her blood urea nitrogen moderately increased reaching 106 mgm per 100 c c in December 1934 She continued to do housework and went with the family in which he worked to North Beverly in the summer of 1935 Here she caught cold became very dyspneic on

the retina Vision often is decreased Blood pressure usually has been normal Fever may be present as in other forms of sarcoidosis

It appears that renal insufficiency is primarily the result of actual mechanical interference with kidney function from the sarcoid lesions in the kidney Prognosis is relatively good, since as with other forms of sarcoidosis regression of the lesions very often occurs When this happens, renal insufficiency and retinal changes lessen and there is a long benign course

Renal Cysts and Polycystic Kidney

Cysts single or multiple, so long as they remain small and uninfected cause no symptoms and have no physical signs With infection they behave as would abscesses Hemorrhage into the small cysts has no clinical effect Renal cysts uninfected and without hemorrhage even though quite large as a rule, remain without symptoms they may or may not be detected on physical examination or they may be palpated as an abdominal tumor With hemorrhage into such cysts there may be local tenderness or pain radiating into the groin region from the tension caused by bleeding into the cyst which is a closed cavity With infection similar tenderness and pain develop and in addition appear the local and general symptoms and signs of infection, particularly fever or chills and fever and leucocytosis as if there was pyelonephritis or pyonephrosis although usually few or no pus cells appear in the urine

With *multiple renal cysts polycystic kidney* sooner or later a tumor mass becomes palpable in each flank Cysts usually are widely scattered especially in the cortex Rarely they may be confined to the medullary part of the kidney[133] Pyelograms give a very characteristic picture so that the roentgenologist often is able to make the correct diagnosis on the basis of this From time to time hematuria may develop With hemorrhage into or infection[410] of, some of these cysts local tenderness and radiating pain appear and with infection the same developments as with infected single cysts As these kidneys enlarge from increased size of the cysts changes in renal function take place The specific gravity of the urine falls and finally becomes fixed at about 1 010 or lower Slight albuminuria develops with a few hyaline casts and from time to time red cells 'Phthalein excretion slowly falls and retention of non protein nitrogen substances becomes evident and increases Disturbances in electrolyte balance are apt to develop Since the pathological changes in renal functioning tissue gradually appear and progress slowly in degree these patients very often show a most remarkable ability to adjust themselves to their renal insufficiency and may be seemingly in actual good health at a level of azotemia in which most patients with other forms of Bright's disease would show numerous symptoms or be in actual uremia These patients toward their end behave much as would a patient from whom a single

was infiltrated with considerable numbers of scattered lymphoid cells There were *scattered collections of polymorphonuclear leucocytes but no definite abscesses* The cysts were lined with a single layer of cuboidal epithelium and contained coarsely granular or finely granular material Many of the arterioles showed considerable thickening with hyalinization although a goodly number were fairly normal

Summary of Case XXIX —This patient in November 1930 developed symptoms of pyelitis and at that time enlarged kidneys were palpated These showed the pyelograms typical of polycystic kidneys At this time there was no albuminuria blood urea nitrogen was normal but there was definite although moderate anemia Three years later (1933) there was renal insufficiency as shown by phthalein excretion of 10 per cent and blood urea nitrogen of 32 mgm per 100 c c Blood pressure had become elevated 170/100 Her urine contained a very little albumin One year later (1934) renal function had decreased more the phthalein excretion now being 2 5 per cent and blood urea nitrogen 60 mgm per 100 c c Blood pressure was 180/95 The patient had lost 20 lbs in weight in 2 years and had shortness of breath In another year (1935) she was more anemic the kidneys were larger urine specific gravity was 1 010 urine showed only a very slight trace of albumin phthalein had become zero and blood urea nitrogen rose to 106 then to 132 mgm per 100 c c Blood pressure reached 210/105 She developed uremic manifestations and she died 5 years after cystic kidneys were detected The striking feature was the steady continuous decrease in renal function with no evidence in the urine of any activity of renal process indicative of a slow steady decrease in the amount of functioning kidney tissue For a long time body functions adapted themselves to this so that symptoms and signs of renal insufficiency were very slight Autopsy showed clearly that this had happened as a result of increasing pressure by enlarging cysts on the intervening kidney with its glomeruli and tubules rendering them increasingly incapable of functioning as renal excretory structures In this patient also the liver was polycystic

With polycystic kidney such dietary and other management as is appropriate for chronic non-edematous Bright s disease should be applied Crises of renal retention may occur and if met by appropriate measure as described elsewhere in Part II of this chapter the patient may be tided over his critical condition back again into reasonable good health At one time exploration of polycystic kidneys with puncture of numerous cysts was advised as a measure to improve renal function by decreasing the pressure of the distended cysts on the adjacent functioning kidney tubules and glomeruli but this form of treatment was not very effective and largely has been abandoned Puncture and drainage of infected cysts after a trial with penicillin or of cysts distended by hemorrhage into them still is advisable in some patients *Some patients have been greatly improved by drainage of infected cysts and lived for many months or years thereafter*[436] Cases have been

exertion began to have swelling of the ankles and commenced to be awakened at night with marked shortness of breath and wheezing Pruritus now developed She coughed a good deal and sometimes raised blood streaked sputum She was nauseated and vomited almost every morning She began to have marked weakness in the extremities and noticed slight puffiness about the eyes but had no blurring of vision no twitching

She came back to the hospital on June 6 1935 Ophthalmoscopic examination now showed rather marked arteriovenous compression one small hemorrhage in the right upper quadrant of the right fundus, no other abnormalities Her heart was considerably enlarged with a blowing systolic murmur and a gallop rhythm There were signs of moderate fluid in both sides of the chest The kidney tumors could be felt in both flanks the right measuring 9 by 9 cm the left 7 by 5 cm The liver edge was felt 5 cm below the costal margin was distinctly tender

Her urine now showed a slight trace of albumin with 15 to 25 white cells and rare casts Specific gravity remained at 1 010 Her hemoglobin was 42 per cent, her red blood cells 2 860 000 Her blood urea nitrogen was 132 mgm per 100 c c Her total plasma protein was 5 6 Pericardial friction rub developed Her blood pressure increased reaching 210 mm Hg systolic 105 diastolic, on June 15 She rapidly declined and died on June 18 1935

Autopsy — Diagnoses congenital polycystic kidneys, cardiac hypertrophy uremic ulcerations of colon and vagina uremic pericarditis pyelitis, right sided, ascites moderate cysts of the liver generalized arterio- and arteriolo-sclerosis

The *heart* weighed 440 grams showed a fibrinous pericarditis considerable atheroma at the base of the aorta and in the coronary arteries but no obstruction of the latter The valves were normal the myocardium seemed pale but not otherwise abnormal

The *liver* weighed 1490 grams showed a moderate number of small cysts thin walled close beneath the capsule and also scattered diffusely throughout all parts of the liver the largest was not over 2 cm in diameter On microscopic study these cysts were found to be lined by a single layer of cuboidal epithelium and contained amorphous granular material About them there was a thin zone of fibrous tissue and slight increase generally of the periportal connective tissue

Kidneys weighed 865 grams right 800 left The entire surface of both kidneys was covered with innumerable cysts of large and small size The renal arteries were markedly sclerotic although showing no calcification On section the cystic nature of the entire substance of both kidneys was disclosed and no definitely normal renal tissue could be seen between the cysts The cysts contained thin fluid varying in color from whitish yellow to bluish red the largest cysts were 4 to 5 cm in diameter others were of decreasing size to 1 mm or less Pelves of both kidneys were moderately distended The urine in the right kidney pelvis was somewhat cloudy and its mucosa considerably inflamed Sections of the kidneys showed very little functional renal tissue and in three sections only three possibly functional glomeruli were seen Glomerular tufts were shrunken their capsules hyalinized and contained cellular débris but apparently no inflammatory exudate A number of glomeruli were more or less completely sclerosed Several narrow bands of tissue were found containing numerous tubules the tubules exhibiting various types of atrophy and dilatation many containing granular and cellular debris Some contain masses of polynuclear leucocytes The fibrosed interstitial tissue

reniculi reduced in number Cysts are not infrequent in these kidneys In some arteriosclerosis or hydronephritis have been causative In many glomeruli are rudimentary or absent The cortex is extremely thin Tubules are closely packed to give under the microscope a thyroid like appearance The other kidney as a rule is enlarged The condition can be recognized by x ray pyelography Unless some disease appears in the non hypoplastic kidney of these patients there are no clinical changes beyond a considerable frequency of hypertension and its associated phenomena

Bilateral renal hypoplasia[472] pathologically shows the same lesions as occur in the unilateral form If the hypoplasia is of marked degree in both kidneys still birth or brief life follows When less marked there are clinical evidences of renal hypofunction causing in early life the clinical picture of chronic non-edematous or azotemic Bright s disease Usually these patients are markedly dwarfed[2 4 3] Relatively few such cases have been reported In early life this form of renal disease may be suspected when there are clinical evidences of marked chronic rapidly progressing renal insufficiency X ray with pyelography can show the small kidney or at least fail to reveal a normally sized kidney shadow

Leptospiral Nephritis

Leptospiral organisms sometimes cause nephritis[466 467] This is of interest in relation to the general problem of the etiology of Bright s disease for it represents a distinctive difference from the far more usual forms of Bright s disease inasmuch as it is not caused by a bacterium and inasmuch as it appears to be the result of the local presence in the kidney of the causative organism instead of the result of a renal allergic mechanism as is usually considered the causative mechanism of Bright s disease It has an analogy in the occasional case of syphilitic Bright s disease where a treponeme is the cause

Leptospira icterohemorrhagiae causes a febrile disease with or without jaundice With either there may be kidney involvement and sometimes there are non icteric patients in whom renal involvement is the chief feature[165 468] It is with the latter form that the true cause of the renal symptomatology more easily can be missed unless the possibility suggested perhaps by a history of swimming in or other contact with water infected by rats with leptospira is considered and tested for by examining the patient s urine for leptospira by guinea pig inoculations or by determining the presence in the patient s serum of agglutinins for the organism In patients with renal involvement from leptospirosis there is oliguria even anuria albuminuria and the urine shows red blood cells leucocytes and casts as in other forms of acute Bright s disease along with the usual symptoms of acute Bright s disease Fever is the rule more persistent than is usual in other forms of acute Bright s disease Blood urea and blood non protein nitrogen are increased

reported in which drainage of infected cysts has been done several times with intervals of relatively good health Polycystic kidney eventually will be fatal, but it is to be remembered that some of these patients will have long years of good health with which to taunt the physician, who early has given a pessimistic opinion of early death In some patients the process just progresses slowly because the cysts either are not very numerous or because they enlarge very slowly There are patients in whom there are fairly numerous cysts of the same type and apparent origin as in polycystic kidney, which are accidental autopsy findings, which never have harmed the patient during life

Large, *so called solitary, cysts of the kidney* may be diagnosed by palpation, and their true nature revealed by x ray or by the type of change which sometimes appears in pyelograms[4 8] If as sometimes happens, calcification of cyst wall has taken place this in the x ray may lead to correct diagnosis[4-8] Frequently a correct diagnosis is only made by surgical exploration This type of renal cyst, when producing symptoms should be treated by excision Sometimes extensive hemorrhage into the cyst will be a factor leading to exploration and excision If infection becomes evident, thorough treatment with penicillin should be carried out This failing to cure as well it may because the penicillin has been poorly excreted into the cyst cavity, surgical drainage is indicated

Renal Agenesis and Hypoplasia

Bilateral agenesis[472] of the kidney obviously i incompatible with life With absences of kidneys ureters usually are completely or partially absent Sometimes the bladder also is absent Still birth is the rule but one reported case lived 11 days Oligohydramnios is usual the amniotic fluid chiefly is fetal urine

Unilateral agenesis[472] of the kidney is reported to occur in from 1 to 400 to 1 to 1 610 postmortems according to different observers Collins[471] collected 572 cases from 337 488 postmortems 1 to 920 One kidney with ureter may be completely absent or with this part or all of the ureter may be present In other patients a rudimentary kidney is present incapable of sustaining life, if the other kidney is removed In the latter a few rudimentary glomeruli and tubules may be seen Arrested development of the mesonephros is the factor underlying renal agenesis

The unilateral normal kidney of these patients usually is larger than normal apparently a work hypertrophy It is widely held that such solitary kidneys are more prone to disease than normal kidneys A unilateral kidney may be recognized by cystoscopic examination or by x ray with pyelogram

Unilateral hypoplasia[4 2] of the kidney may result from defective development (true hypoplasia) or from secondary atrophy caused by urinary obstruction, arteriosclerosis or chronic interstitial inflammation Often these kidneys have no functioning parenchyma, but they may have normal microscopic structure with

using arsenicals and recently seen from the use of penicillin[445, 461, 4 9] This form of syphilitic Bright s disease develops in the earlier weeks of the secondary stage of syphilis sometimes later and seems to be a part of the generalized stage of syphilis *with or soon following syphilitic mucocutaneous lesions The nature of the* pathological lesions in these patients is not well known An occasional autopsy as in Munk s patient has shown a large grayish white kidney with lipoid deposits in tubules and cells of the interstitial tissue and glomeruli showing very little change In these kidneys there was nothing suggestive of syphilitic etiology Clinically generalized edema of varying degree urine containing a large amount of albumin and moderate hypoproteinemia are the evidences of kidney involvement It is the same clinical picture as already has been described under the heading *Acute Subacute and Chronic Edematous Bright s Disease Nephrotic Type* This form of syphilitic renal disease was known to earlier syphilologists who among other features emphasized that the urine contained a relatively large amount of globulin which some of them thought diagnostic of syphilitic etiology and that cure followed treatment with iodide and mercury this being before the advent of arsphenamine therapy Later arsphenamine was reported to be effective Recently the importance of it has been re-emphasized by reported prompt cure from the use of penicillin The latter is of very great general interest because it seems that this is the only form of Bright s disease in which the medical profession possesses an effective cure a specific therapy One report[438] however suggests that penicillin has cured acute nephritis with prominent edema in which syphilis was not the cause

The great importance of the recognition that syphilis may be the etiological factor in a patient with edematous Bright s disease is obvious now that prompt cure from the use of penicillin may be expected. In any patient with this form of Bright s disease careful search should be made for evidences of any sort that the patient has had infection with syphilis If such evidences are found or even suspicioned penicillin should be given promptly in large dosage Even if syphilis is not the cause penicillin will do no injury to the kidney it may be effective according to one report[438] even when syphilis is not the cause

Surprisingly little is known of the pathological lesions in the kidney caused by and specific for syphilis Gummata may occur but are rare Perivascular mononuclear cell (lymphocytic) infiltration as in other organs sometimes is found with or without endarteritis Many of the earlier syphilologists were skeptical of their occurrence as Frerichs (1851) Spiess (1877) Rosenstein (1894) while others believed in their infrequent occurrence or that syphilis had some role in the etiology of nephritis Rayer (1840) Virchow (1858) Lanceraw (1866) Beer (1867) Mauriac (1890) Furbringer (1885) Freytag (1898) Karvonen (1901) Hoffmann (1902) and many others

Many pathologists have considered renal amyloidosis as a manifestation of

and 'phthalein excretion is decreased Leptospira may be found in the urine as early as the sixth day of the disease and may persist for weeks However they are not always found in the urine, even by guinea pig inoculations Agglutinins may be demonstrated in both urine and blood serum, in 100 cases Davidson and Smith[467] demonstrated agglutinins in the urine in 16 6 per cent during the first week, in 71 4 per cent during the second, in 91 8 per cent during the third and in 100 per cent after the third week In fatal cases there has been focal interstitial nephritis in swollen kidneys Tubular epithelium is swollen, granular, sometimes necrotic Glomerular lesions usually are slight In many bile pigmentation is prominent Stiles Goldstein and McCann[465] recently have reported two patients from Rochester N Y with spirochetal nephritis For treatment a ketogenic diet and mandelic acid to produce acidification of the urine is suggested Sulfonamides and penicillin seem to have had little or no effect

The Kidney in Syphilis

In the active stages of secondary syphilis or the period of treponematemia albuminuria, sometimes with a few to moderate number of red blood cells in the urine, is found in 3 to 4 up to 7 to 8 per cent of these patients according to various reports However it is the rule for these changes in the urine to clear and leave no subsequent symptoms or signs of renal damage This is analogous to what happens in other forms of acute infectious disease and, as in these hardly merits the term nephritis or Bright's disease

Perhaps a rare patient will show more prolonged albuminuria and a greater degree of hematuria to justify the term acute Bright s disease of the hemorrhagic type It is not certain however, that these patients do not represent a complicating acute Bright's disease of other etiology At any rate no satisfactory proof of syphilis as cause of the renal lesion in them has been adduced The finding in the urine of any of these patients of treponema pallidum has been infrequent, and when treponemata have been reported, there is doubt of the correctness of the assumption that they are treponemata specific for syphilis

There is however, a form of acute or subacute edematous Bright's disease infrequent in occurrence, which seems undoubtedly to be of syphilitic etiology[445, 451, 474, 477, 478, 479] This form of syphilitic Bright's disease has been recognized for a long time In 1867 Beer[450] included it in his classification as rein parenchymatose nephritis Neumann (1896) Karvonen (1898) and Hoffmann (1902) recognized it All seem to consider it rare of occurrence Evidence of the causative role of syphilis in this form of Bright s disease lies in its occurrence in patients with lesions characteristic of syphilis and with serological tests positive for syphilis and, more important a prompt response to antisyphilitic therapy as noted by earlier syphilologists using potassium iodide and mercury[474], later ones

using arsenicals and recently seen from the use of penicillin[44, 451, 4, 9] This form of syphilitic Bright s disease develops in the earlier weeks of the secondary stage of syphilis sometimes later, and seems to be a part of the generalized stage of syphilis *with or soon following syphilitic mucocutaneous lesions* *The nature of the* pathological lesions in these patients is not well known An occasional autopsy as in Munk s patient has shown a large grayish white kidney with lipoid deposits in tubules and cells of the interstitial tissue and glomeruli showing very little change In these kidneys there was nothing suggestive of syphilitic etiology Clinically generalized edema of varying degree urine containing a large amount of albumin and moderate hypoproteinemia are the evidences of kidney involvement It is the same clinical picture as already has been described under the heading *Acute, Subacute and Chronic Edematous Bright s Disease Nephrotic Type* This form of syphilitic renal disease was known to earlier syphilologists who among other features emphasized that the urine contained a relatively large amount of globulin which some of them thought diagnostic of syphilitic etiology and that cure followed treatment with iodide and mercury this being before the advent of arsphenamine therapy Later arsphenamine was reported to be effective Recently the importance of it has been re emphasized by reported prompt cure from the use of penicillin The latter is of very great general interest because it seems that this is the only form of Bright s disease in which the medical profession possesses an effective cure a specific therapy One report[438] however suggests that penicillin has cured acute nephritis with prominent edema in which syphilis was not the cause

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Many pathologists have considered renal amyloidosis as a manifestation of

syphilis in some patients with albuminuria According to them the edematous form of Bright's disease, already discussed results in part or entirely from amyloidosis, a view not held at present, although amyloidosis of any cause including syphilis can cause this clinical picture Rich[175] has described a renal lesion seemingly caused by syphilis in patients in the late or tertiary stage of syphilis, especially often in patients with syphilitic aortitis The lesion was ' found in 6 5 per cent of 200 autopsies in which there were definite syphilitic lesions in other organs and in 5 additional cases in which no other syphilitic lesion was found at autopsy but in which there was definite clinical proof of the existence of syphilis (positive Wassermann reaction)" The lesion macroscopically appears as minute, glistening, grayish yellow flecks scattered here and there beneath the capsule and in the cortex Microscopically there are dense, focal accumulations of mononuclear cells situated in the interstitial tissue, especially of the cortex There are also distinctly perivascular, mononuclear accumulations about the vessels of the kidney The cells are mainly small lymphocytes, but also present are large lymphocytes macrophages and plasma cells sometimes a few eosinophiles These cells tend to gather into sharply outlined spherical nodules which encroach upon, and project into tubules With degenerative changes fat laden macrophages and cholesterin crystals appear, some of which later are surrounded by foreign body giant cells Eventually fibrosis and scarring result Glomeruli may be caught in the lesion, but glomeruli are not primarily involved What Rich has described may be what Beer[160] in 1867 included in his classification as 'zirkum skripte zellige Knoten (kleine 'Gummen) in der Rinde"

Clinically the cases studied by Rich showed only slight evidences of Bright's disease none showed the picture of edematous Bright's disease or Bright's disease with the nephrosis syndrome

There is very little definite clinical evidence that syphilis causes chronic non edematous Bright's disease Possibly some of the scarring and some of the vascular lesions shown in the kidneys of patients with late syphilis can be regarded as of syphilitic etiology Antisyphilitic treatment does not seem to benefit these patients but penicillin has not been used up to the present Very possibly the kidney lesions in these patients are coincidental rather than caused by syphilis The same seems true of the acute subacute and chronic glomerular lesions found sometimes in patients in different stages of syphilis Many believe that secondary infection of syphilitic lesions by pyogenic bacteria is the etiological factor in these patients At any rate the lesions in the glomeruli have no appearances different from those seen in patients with various forms of glomerular lesions and no evidences of syphilitic infection However many syphilologists do believe that syphilis is causative in patients developing clinical evidences of chronic non edematous Bright's disease who at autopsy show small scarred kidneys with the histological changes of chronic vascular nephritis

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